PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C07D 241/44, 401/04
C07C 233/54, 251/38
A61K 31/495

A1

(11) International Publication Number: WO 92/1124

(43) International Publication Date: 9 July 1992 (09.07.9)

(21) International Application Number: PCT/US91/08586

(22) International Filing Date: 22 November 1991 (22.11.91)

(30) Priority data:
631,139 20 December 1990 (20.12.90) US

(60) Parent Application or Grant
(63) Related by Continuation
US 631,139 (CIP)
Filed on 20 December 1990 (20.12.90)

(71) Applicant *(for all designated States except US)*: WARNER-LAMBERT COMPANY [US/US]; 2800 Plymouth Road, Ann Arbor, MI 48105 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : HAYS, Sheryl, Jeanr [US/US]; 1080 Bandera Drive, Ann Arbor, MI 481C (US). JOHNSON, Graham [GB/US]; 1130 Bande Drive, Ann Arbor, MI 48103 (US). LESCOSKY, L onard, Joseph [US/US]; 328 Fifth Street, Ann Arbo MI 48103 (US). MALONE, Thomas, Charles [US/US 45139 North Spring Drive, Canton, MI 48187 (US). NC VAK, Perry, Michael [US/US]; 3327 Burbank Driv Ann Arbor, MI 48105 (US).

(74) Agents: THIERSTEIN, Joan; Warner-Lambert Compan 2800 Plymouth Road, Ann Arbor, MI 48105 (US) et a

(81) Designated States: AT (European patent), AU, BE (Eur pean patent), CA, CH (European patent), DE (Eur pean patent), DK (European patent), ES (European pa tent), FI, FR (European patent), GB (European patent GR (European patent), IT (European patent), JP, KI LU (European patent), NL (European patent), NO, S (European patent), US.

Published
With international search report.

(54) Title: 2-ACYLAMIDO DERIVATIVES OF 3,4-DIHYDRO-3-OXO-QUINOXALINE HAVING PHARMACEUTICAL ACTIVITY

(57) Abstract

The present invention relates to novel 2-acylamide derivatives of 3,4-dihydro-3-oxo-quinoxaline useful as pharmaceutica agents, to methods for their production, to pharmaceutical compositions and methods of treatment therefor. The compounds o the present invention have activity as excitatory amino acid receptor mediators and, thus, are useful in the treatment of a wid range of neurodegenerative disorders including cerebrovascular disorders such as stroke.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinea	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland	KR	Republic of Korea	SN	Senegal
CI	Côte d'Ivoire	LI	Liechtenstein	SU+	Soviet Union
CM	Cameroon	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
DE*	Germany	MC	Monaco	US	United States of America
DK	Denmark				

+ Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.

2-ACYLAMIDO DERIVATIVES OF 3,4-DIHYDRO-3-OXO-QUINOXALINE HAVING PHARMACEUTICAL ACTIVITY

BACKGROUND OF THE INVENTION

The present invention relates to novel 2-acylamides of 3,4-dihydro-3-oxo-quinoxaline useful as pharmaceutical agents, to methods for their production, to pharmaceutical compositions and to methods of use therefor.

The compounds of the present invention are active as mediators of excitatory amino acid receptors. Such activity is useful in the treatment of neurodegenerative disorders including cerebrovascular disorders as well as in the treatment of schizophrenia, Parkinson's disease, or epilepsy; and as analgesics and anxiolytics.

Excessive excitation by neurotransmitters can cause the degeneration and death of neurons. It is believed that this degeneration is in part mediated by the excitotoxic actions of glutamate and aspartate at the N-methyl-D-aspartate (NMDA) receptor. This excitotoxic action is responsible for the loss of neurons in cerebrovascular disorders such as cerebral ischemia or cerebral infarction known as at least part of a range of conditions, such as thromboembolic or hemorrhagic stroke, cerebral vasospasm, hypoglycemia, cardiac arrest, status epilepticus, perinatal asphyxia, anoxia such as from drowning, pulmonary surgery and cerebral trauma.

There are no specific therapies for these neurodegenerative diseases; however, compounds which act specifically as antagonists of the NMDA receptor

complex, either competitively or noncompetitively, offer a novel therapeutic approach to these disorders:

R. Schwarcz and B. Meldrum, The Lancet 140 (1985);

B. Meldrum in "Neurotoxins and Their Pharmacological Implications" edited by P. Jenner, Raven Press, New York (1987);

D. W. Choi, Neuron 1:623 (1988).

Confirmation of the protective effects of noncompetitive NMDA antagonists in various pharmacological models of neurodegenerative disorders have appeared in the literature:

J. W. McDonald, F. S. Silverstein, and M. V. Johnston, Eur. J. Pharmocol. 140:359 (1987);

R. Gill, A. C. Foster, and G. N. Woodruff, J. Neurosci. 7:3343 (1987);

S. M. Rothman, J. H. Thurston, R. E. Hauhart, G. D. Clark, and J. S. Soloman, Neurosci. 21:673 (1987);

M. P. Goldbert, P-C. Pham, and D. W. Choi, Neurosci. Lett. 80:11 (1987);

L. F. Copeland, P. A. Boxer, and F. W. Marcoux, Soc. Neurosci. Abstr. 14 (part 1):420 (1988);

J. A. Kemp, A. C. Foster, R. Gill, and G. N. Woodruff, TIPS 8:414 (1987);

R. Gill, A. C. Foster, and G. N. Woodruff J. Neurosci. 25:847 (1988);

C. K. Park, D. G. Nehls, D. I. Graham, G. M. Teasdale, and J. M. McCulloch, Ann. Neurol. 24:543 (1988);

G. K. Steinburg, C. P. George, R. DeLaPlaz, D. K. Shibata, and T. Gross, Stroke 19:1112 (1988);

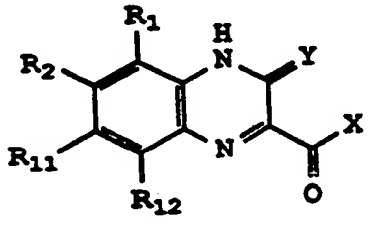
J. F. Church, S. Zeman, and D. Lodge, Anesthesiology 69:702 (1988).

U.S. Patent Number 4,181,724 discloses certain acids and esters of quinoxalinone compounds useful for asthma, eczema, or urticaria in animals. U.S. Patent Nos. 4,210,647 and 4,264,600 and European Patent Publication No. 010,426 disclose more specifically substitutions on acids and esters of quinoxalinone compounds that are useful as antivirals, especially against influenza viruses. The further preparation of these compounds is as in Japanese application 1075-474-A described in Derwent Abstract No. 89-132587/18. Quaternary ammonium salts of certain acids of quinoxalinone compounds are also disclosed as antivirals in U.S. 4,252,954. Amido derivatives of quinoxalinones are substituents of alkylarylsulfonylureas for use in hypoglycemia in Belgium Patent No. 764,998 and also are substituents of cephalosporins for use as antibacterials in European Application No. 304,158.

Each of these references differs from the present invention by the hydroxamate; amide; acyl urea; acyl carbamate; imide; acyl sulfonamide; or hydrazine derivatives of the quinoxalinone as disclosed herein.

SUMMARY OF THE INVENTION

The present invention provides compounds of the formula



I

or tautomers thereof; or a pharmaceutically acceptable base or acid addition salt thereof; wherein

(1) Y is oxygen or sulfur;

(2) R_1, R_2, R_{11}, and R_{12} are independently hydrogen, lower alkyl, halogen, trifluoromethyl, cyano, nitro, methylthio, lower alkenyl, lower alkynyl, SO_2NH_2, $S(O)_{1-2}R$ wherein R is hydrogen or lower alkyl, OCF_3, or two of R_1, R_2, R_{11}, and R_{12} can be taken together to form a carbocyclic ring of six carbons, or can be taken together to form a heterocyclic or heteroaryl ring wherein the heteroatom is oxygen, sulfur, or nitrogen, and wherein the carbon on the carbocyclic ring is optionally further substituted by one of R_1, R_2, R_{11}, or R_{12};

(3) X is

(a) $NR^6SO_2R^3$,

(b) NR^6R^3 with the proviso that one of R^6 and R^3 must be other than hydrogen and at the same time one of R_1, R_2, R_{11}, and R_{12} must be other than hydrogen,

(c) NR^6OR^3,

(d) $NR^6CONR^3R^4$ with the proviso that one of R^3 and R^4 must be other than hydrogen,

(e) NR^6COR^5,

(f) $NR^6CO_2R^3$,

(g)

(h)

(i) an amino acid residue which is phenylglycine, phenylalanine, alanine, leucine, isoleucine, proline, or valine,

(j) lower alkyl esters of the amino acid residue as defined above;

wherein

i) R^3 and R^4 are independently

1) hydrogen;

2) alkyl of from one to twenty carbons, preferably one to twelve carbons;

3) alkenyl of from three to twenty carbons, preferably three to twelve carbons;

4) alkynyl of from three to twenty carbons, preferably three to twelve carbons;

5) aryl which is phenyl, indenyl, or naphthyl wherein phenyl is

aa) unsubstituted or

bb) substituted by one to five of lower alkyl or halogen, or

cc) substituted by one to three of

xxi) trifluoromethyl,

xxii) nitro,

xxiii) amino,

xxiv) mono- or di-lower alkylamino,

xxv) hydroxy,

xxvi) lower alkoxy,

xxvii) carboxy, or

xxviii) $NHCOR^5$ wherein R^5 is independently as defined below,

xxix) $NHCOAlk_{1-6}$ wherein Alk_{1-6} is lower alkyl,

xxx) $NHSO_2R^5$ wherein R^5 is independently as defined herein,

xxxi) CN,

xxxii) $CONR^5R^6$ wherein R^5 and R^6 are independently as defined herein,

xxxiii) $S(O)_{0-2}R^5$ wherein R^5 is independently defined herein,

xxxiv) $-CR^5$;

6) arylloweralkyl;

7) arylloweralkenyl;

8) heterocycle;

9) heteroaryl;

10) $(CH_2)_qR^7$ wherein q is an integer of one to four and R^7 is

(A) heterocycle,

(B) heteroaryl,

(C) SO_2R^8 wherein R^8 is hydrogen or lower alkyl and R is independently as defined herein,

(D) PO_3R^8 wherein R^8 is as defined above,

(E) CO_2R^8 wherein R^8 is as defined above, or

(F) NR^9R^{10} wherein R^9 and R^{10} are independently hydrogen or

alkyl or R^9 and R^{10} are taken together to form a heteroaryl ring; or

11) an amino acid residue as defined above;

ii) R^5 is

1) hydrogen,
2) lower alkyl,
3) lower alkenyl,
4) aryl,
5) aryllowеralkyl,
6) aryllowеralkenyl,
7) heteroaryl or
8) heteroaryllowеralkyl;

iii) R^6 is

1) hydrogen or
2) lower alkyl, preferably hydrogen.

The preferred compounds of the present invention include but are not limited to the compounds of Formula I wherein R_2 and R_{11} are chloro, Y is oxygen, and X is $NHS(O)_2CH_3$, $NHS(O)_2$phenyl, or $NHS(O)_2(CH_2)_4H$.

The more preferred compounds of the present invention are 6,7-dichloro-3,4-dihydro-3-oxo-N-[phenylsulfonyl]-2-quinoxalinecarboxamide and 6,7-dichloro-3,4-dihydro-N-(methylsulfonyl)-3-oxo-2-quinoxalinecarboxamide.

The present invention also includes a pharmaceutical composition for the use of treating cerebrovascular disorders, treating disorders responsive to the blockade of glutamic and aspartic acid receptors, or treating cerebral ischemia, cerebral infarction, cerebral vasospasm, hypoglycemia, cardiac arrest, status epilepticus, cerebral trauma, schizophrenia, epilepsy, neurodegenerative disorders,

Parkinson's disease, Alzheimer's disease, or Huntington's disease comprising a therapeutically effective amount of a compound of Formula I together with a pharmaceutically acceptable carrier.

The present invention also includes a method for treating cerebrovascular disorders which comprises administering to a patient in need thereof the above pharmaceutical composition in unit dosage form.

The present invention also includes a method for treating disorders responsive to the blockade of glutamic and aspartic acid receptors comprising administering to a patient in need thereof a therapeutically effective amount of the above composition in unit dosage form.

The invention also includes a method for treating cerebral ischemia, cerebral infarction, cerebral vasospasm, hypoglycemia, cardiac arrest, status epilepticus, cerebral trauma, schizophrenia, epilepsy, neurodegenerative disorders, Parkinson's disease, Alzheimer's disease, or Huntington's disease comprising administering to a patient in need thereof a therapeutically effective amount of the above composition in unit dosage form.

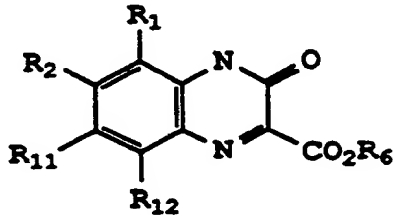
The invention also includes a method for treating stroke in patients in need thereof which comprises administering to a patient in need thereof a therapeutically effective amount of the above composition in unit dosage form.

The invention also includes using as an anesthetic or using together with an anesthetic the above composition in surgical operations where a risk of cerebrovascular damage exists.

The invention further includes processes for the preparation of compounds of Formula I wherein one of the novel intermediates of the Formula II' wherein R_6

is hydrogen are treated to obtain selected corresponding compounds of the Formula I. Further, the compounds of the Formula IV are treated to obtain compounds of Formula I.

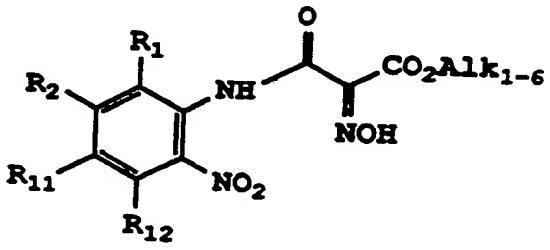
The invention still further includes novel intermediates useful in the processes. The novel intermediate of the present invention is a pure compound of the formula (II')



II'

wherein R_1 and R_{11} are as defined above with the proviso that R'_2 and R'_{12} are independently hydrogen or halogen with the proviso that at least one of R'_2 and R'_{12} are halogen, and R_6 is as defined herein.

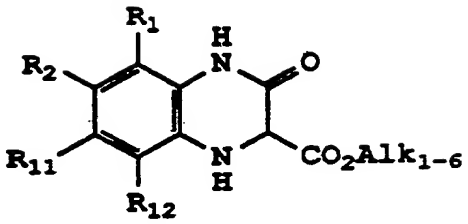
A novel intermediate of the present invention is also a compound of the Formula V



V

wherein R_1, R_2, R_{11}, and R_{12} are as defined above and Alk_{1-6} is lower alkyl.

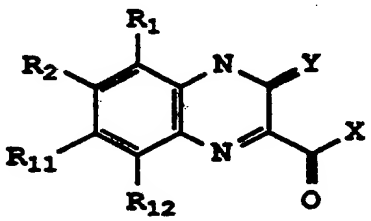
An additional novel intermediate of the present invention is a compound of the Formula (IV)



IV

wherein R_1, R_2, R_{11}, R_{12}, and Alk_{1-6} are as defined above.

Further, the present invention is a process for the preparation of a compound of the Formula (L)

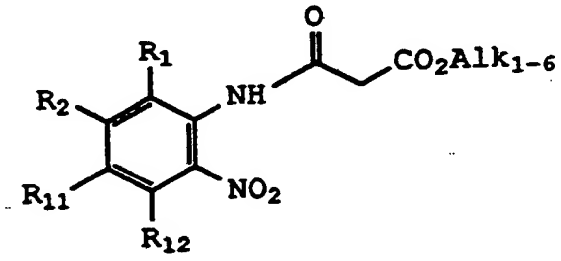


L

wherein R_1, R_2, R_{11}, R_{12}, X, and Y are as defined above.

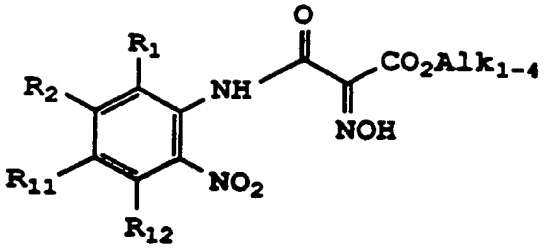
The present invention is a process which comprises

1) treating a compound of the Formula (VI)



VI

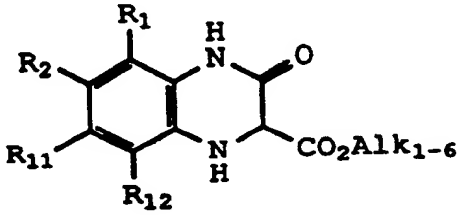
with sodium nitrite to obtain a compound of the Formula V



V

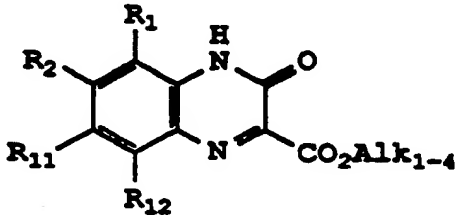
then

2) treating the compound of the Formula V of Step 1) with hydrogen over Raney nickel and then with $TiCl_3$ to obtain a compound of the Formula IV



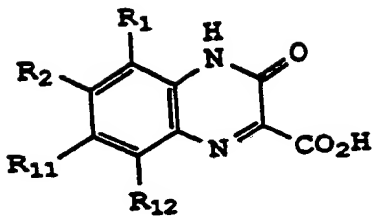
IV

3) treating the compound of the Formula IV of Step 2) with n-bromosuccinimide, bromine, NaOCl, or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DOQ) in an inert solvent to obtain a compound of the Formula (II'_1)



II'_1

4) hydrolyzing the compound of the Formula II'_1 with a hydroxide such as sodium or potassium hydroxide; to obtain the compound of the Formula (II'_2)



II'$_2$

wherein R_1, R_2, R_{11}, and R_{12} are as defined above and Alk_{1-6} is lower alkyl.

This process is shown in Scheme E hereinafter.

DETAILED DESCRIPTION

Loweralkyl means a straight chained or branched chain of from one to four carbon atoms including but not limited to methyl, ethyl, propyl, butyl.

Loweralkenyl means a group from two to four carbon atoms, for example, but not limited to ethylene, 1,2- or 2,3-propylene, 1,2- 2,3-, or 3,4-butylene.

Loweralkynyl means a group from two to four carbon atoms, for example, but not limited to ethynyl, 2,3-propynyl, 2,3-, or 3,4-butynyl; propynyl is the preferred group.

Cycloalkylloweralkyl means cycloalkyl of from three to six carbon atoms and lower alkyl as above, meaning for example, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl; cyclopropylmethyl is the preferred group.

Loweralkoxy means a group of from one to four carbon atoms, for example, but not limited to methoxy, ethoxy, propoxy; methoxy is the preferred group.

Halogen is fluorine, chlorine, bromine, or iodine; fluorine, chlorine and bromine are the preferred groups.

Arylloweralkyl means aryl as defined above and alkyl as defined above, for example, benzyl, 2-phenylethyl, 3-phenylpropyl; preferred groups are benzyl and the benzyl or phenyl is as substituted above.

Arylloweralkenyl means aryl as defined above and alkenyl as defined above, for example, 2-phenylethenylenyl, 3-phenylpropenylenyl; preferred groups are 2-phenylethenylenyl and the phenyl is as substituted above.

Monoloweralkylamino means a group containing from one to four carbon atoms, for example, but not limited to methylamino, ethylamino, n- or i-(propylamino or butylamino).

Diloweralkylamino means a group containing from one to four carbon atoms in each lower alkyl group, for example, but not limited to dimethylamino, diethylamino, di-(n-propyl)-amino, di-(n-butyl)-amino, or may represent a fused ring, for example piperidine.

Heteroaryl means a 5- or 6-membered monocyclic, bicyclic, or fused bicyclic heteroaryl. The monocycle or fused bicyclic aromatic ring contains at least 1 to 4 heteroatoms in at least one ring, such as nitrogen, oxygen, or sulfur or a combination thereof. Such a heteroaryl group includes, for example, thienyl, benzothienyl, furanyl, benzofuranyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolyl, pyrazolyl, isothiazolyl, thiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, imidazolyl, benzothiazolyl, indolyl, quinolinyl, isoquinolinyl, or N-oxides of heteroaryl containing a nitrogen atom.

More specifically, such a heteroaryl may be a 2- or 3-thienyl; which may further be substituted by, for example, a 2-, 3-, or 4-pyridyl ring; 2- or 3-furanyl; 2-, or 3-, or 4-pyridyl or -pyridyl-N-oxide; 2-, 4-,

or 5-pyrimidinyl; 3- or 4-pyridazinyl; 2-pyrazinyl; 2-pyrazinyl-N-oxide; 2- or 3-pyrrolyl; 3-, 4-, or 5-pyrazolyl; 2-, 4-, or 5-oxazolyl; 2-, 4-, or 5-thiazolyl; 3-, 4-, or 5-isoxazolyl; 3-, 4-, or 5-isothiazolyl; 5-tetrazolyl; 3- or 5-(1,2,4,-)triazolyl; 4- or 5-(1,2,3-)triazolyl; 2-, 4-, or 5-imidazolyl; 2-, 3-, 4-, 5-, 6-, or 7-indolyl; 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl; 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolinyl; 2-, 4-, 5-, 6-, or 7-benzothiazolyl; 2-, 3-, 4-, 5-, 6-, or aryl, 7-benzothienyl 1,2-benzisoxazol-3-yl.

Heterocycle means piperidine, piperazine, tetrahydropyridine, tetrahydropyranyl, pyrrolidinyl, pyrazolidinyl, oxazolidinyl, tetrahydrofuranyl, tetrahydrothienyl, and the like. Particularly included are N-piperidine and N-piperazine, which may be further substituted by phenyl.

Well-known protecting groups and their introduction and removal may be used according to the skill in the art and are described, for example, in J. F. W. McOmie, Protective Groups in Organic Chemistry, Plenum Press, London, New York (1973), and T. W. Greene, Protective Groups in Organic Synthesis, Wiley, New York (1981).

The compounds of the present invention contain asymmetric carbon atoms. The instant invention includes the individual diastereomers and enantiomers, which may be prepared or isolated by methods known to those skilled in the art.

Selected compounds of the present invention can exist also as syn and anti forms and are also the present invention.

Any resulting racemate can be resolved into the optical antipodes by known methods, for example by separation of the diastereomeric salts thereof, with

an optically active acid, and liberating the optically active amine compound by treatment with a base. Racemic compounds of the present invention can thus be resolved into their optical antipodes e.g., by fractional crystallization of d- or l-(tartarates, mandelates, or camphorsulfonate) salts. The compounds of the instant invention may also be resolved by the formation of diastereomeric amides or amides by reaction the compounds of the instant invention with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-)-camphanic acid or by the formation of diastereomeric carbamates by reaction of the compounds of the instant invention with an optically active chloroformate or the like.

Additional methods for resolving optical isomers, known to those skilled in the art may be used, for example those discussed by J. Jaques, A. Collet, and S. Wilen in Enantiomers, Racemates, and Resolutions, John Wiley and Sons, New York (1981).

Salts of the compounds of the invention are preferably pharmaceutically acceptable salts. The compounds of the invention are basic amines from which acid addition salts of pharmaceutically acceptable inorganic or organic acids such as strong mineral acids, for example, hydrohalic, e.g., hydrochloric or hydrobromic acid; sulfuric, phosphoric or nitric acid; aliphatic or aromatic carboxylic or sulfonic acids, e.g., acetic, propionic, succinic, glycolic, lactic, malic, tartaric, gluconic, citric, ascorbic, maleic, fumaric, pyruvic, pamoic, nicotinic, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, benzene-sulfonic, p-toluenesulfonic, or napthlenesulfonic acid can be prepared.

Selected compounds of the invention are also acids from which base salts may be prepared.

Likewise, hydrates of compounds of the invention; for which hydrates may exist, are also the present invention.

The compounds of the instant invention exhibit valuable pharmacological properties by selectively blocking the N-methyl-D-aspartate sensitive excitatory amino acid receptors in mammals. The compounds are thus useful for treating diseases responsive to excitatory amino acid blockade in mammals.

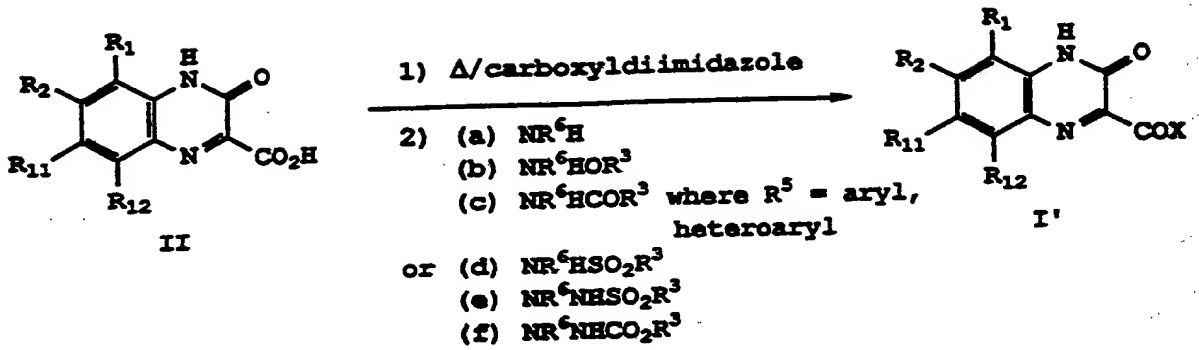
Such disorders include but are not limited to cerebral ischemia or cerebral infarction resulting from a range of conditions such as thromboembolic or hemorrhagic stroke, cerebral vasospasm, hypoglycemia, cardiac arrest, status epilepticus, perinatal asphyxia, anoxia such as from drowning, pulmonary surgery, and cerebral trauma. Other treatments are for schizophrenia, epilepsy, spasticity, neurodegenerative disorders such as Parkinson's disease, Alzheimer's disease or Huntington's disease, Olivo-pontocerebellar atrophy, spinal cord injury, and poisoning by exogenous NMDA poisons (e.g., some forms of lathyrism). Further uses are as analgesics and anesthetics, particularly for use in surgical procedures where a finite risk of cerebrovascular damage exists.

The effects are demonstrable in in vitro tests or in vivo animal tests using mammals or tissues or enzyme preparations thereof, e.g., mice, rats, or monkeys. The compounds are administered to patients enterally or parenterally, for example, orally, transdermally, subcutaneously, intravenously, or intraperitoneally. Forms include but are not limited to gelatin capsules, or aqueous suspensions or

solutions. The applied in vivo dosage may range between about 0.01 to 100 mg/kg, preferably between about 0.05 and 50 mg/kg, most preferably between about 0.1 and 10 mg/kg.

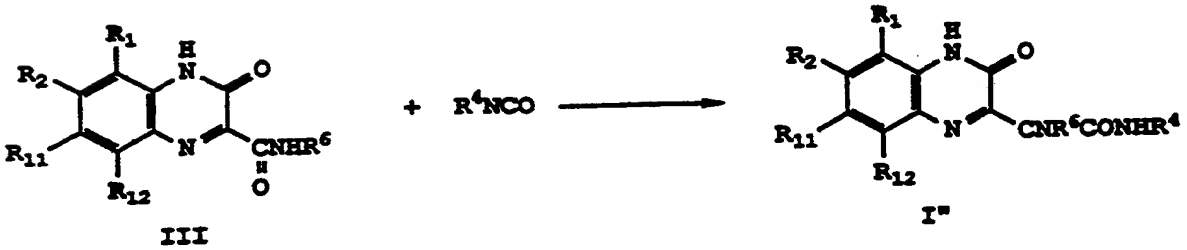
Methods of synthesis of the compounds of the instant invention are illustrated in Schemes A, B, and C. The preparation of compounds of the Formula I' wherein X is $NR^6SO_2R^3$, NR^6R^3, NR^6OR^3, NR^6COR^5, $NR^6NHSO_2R^3$, $NR^6NHCO_2R^3$ or $NR^6CO_2R^3$ and R_{11}, R_{12}, and R_1, R_2, R^3, R^4, R^5, and R^6 are as previously defined and are illustrated in Schemes A and B.

Scheme A



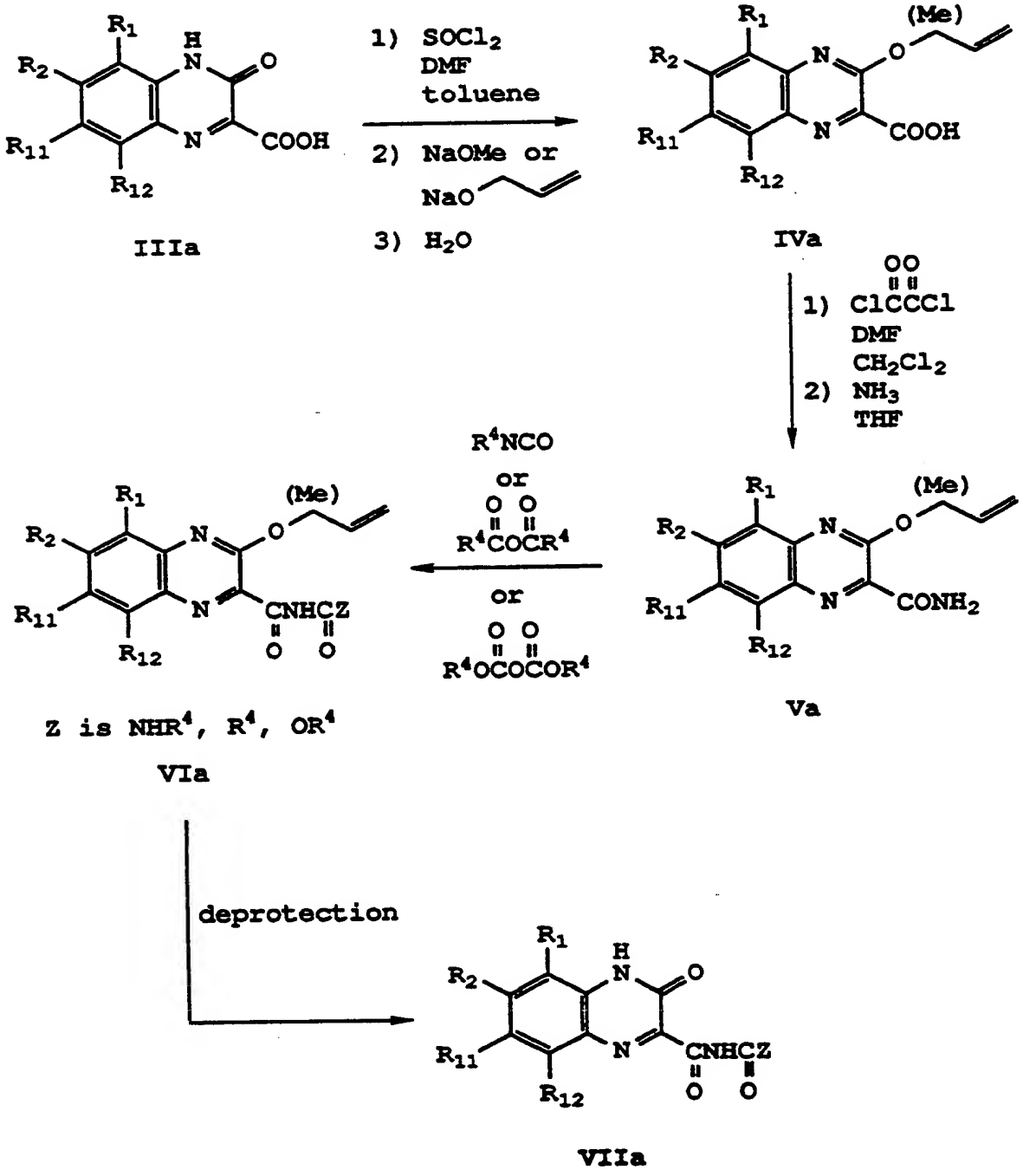
Further, preparation of compounds of the Formula I wherein X is $NHCONR^3R^4$ and R^3 is H and R_1, R_2, R_{11}, R_{12}, and R^4 are as previously defined are illustrated in Scheme B.

Scheme B



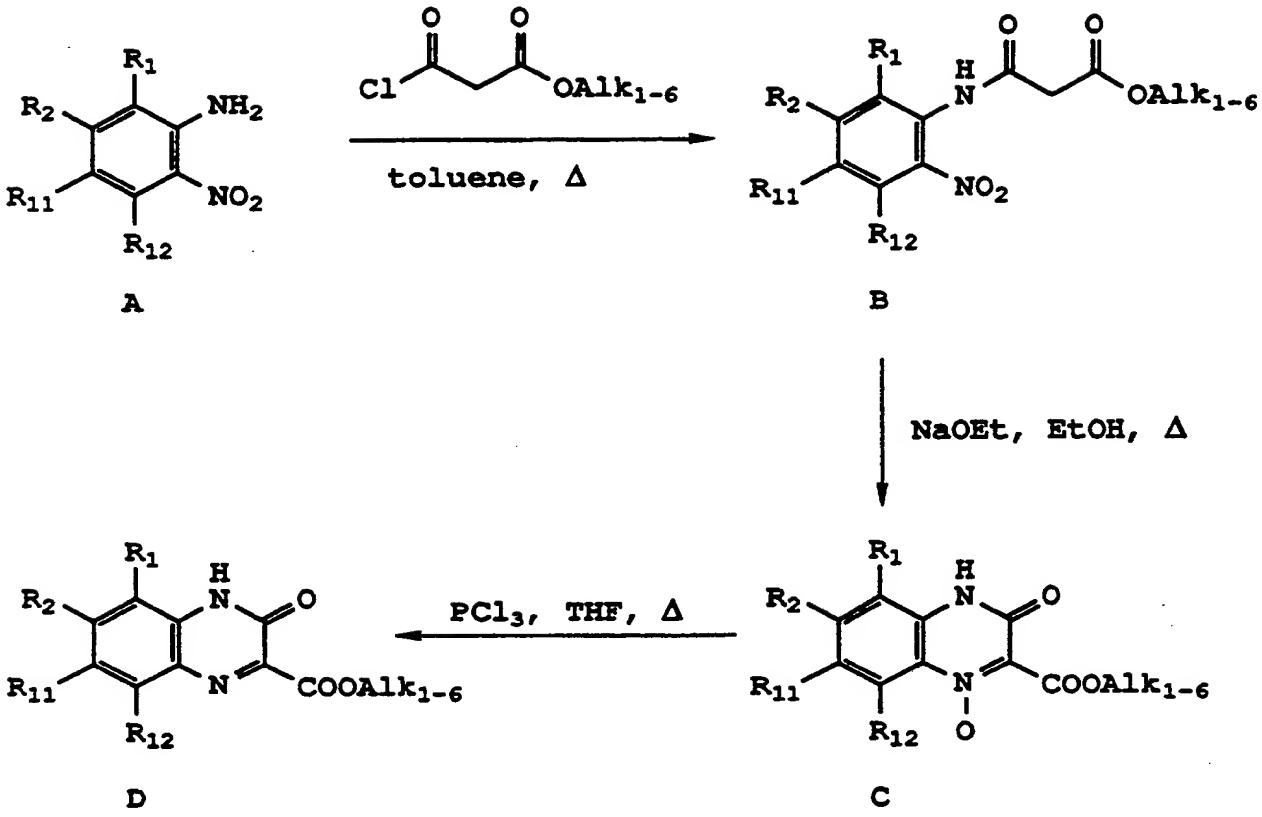
The preferred method for making compounds of Formula I'' is shown in Scheme C.

Scheme C



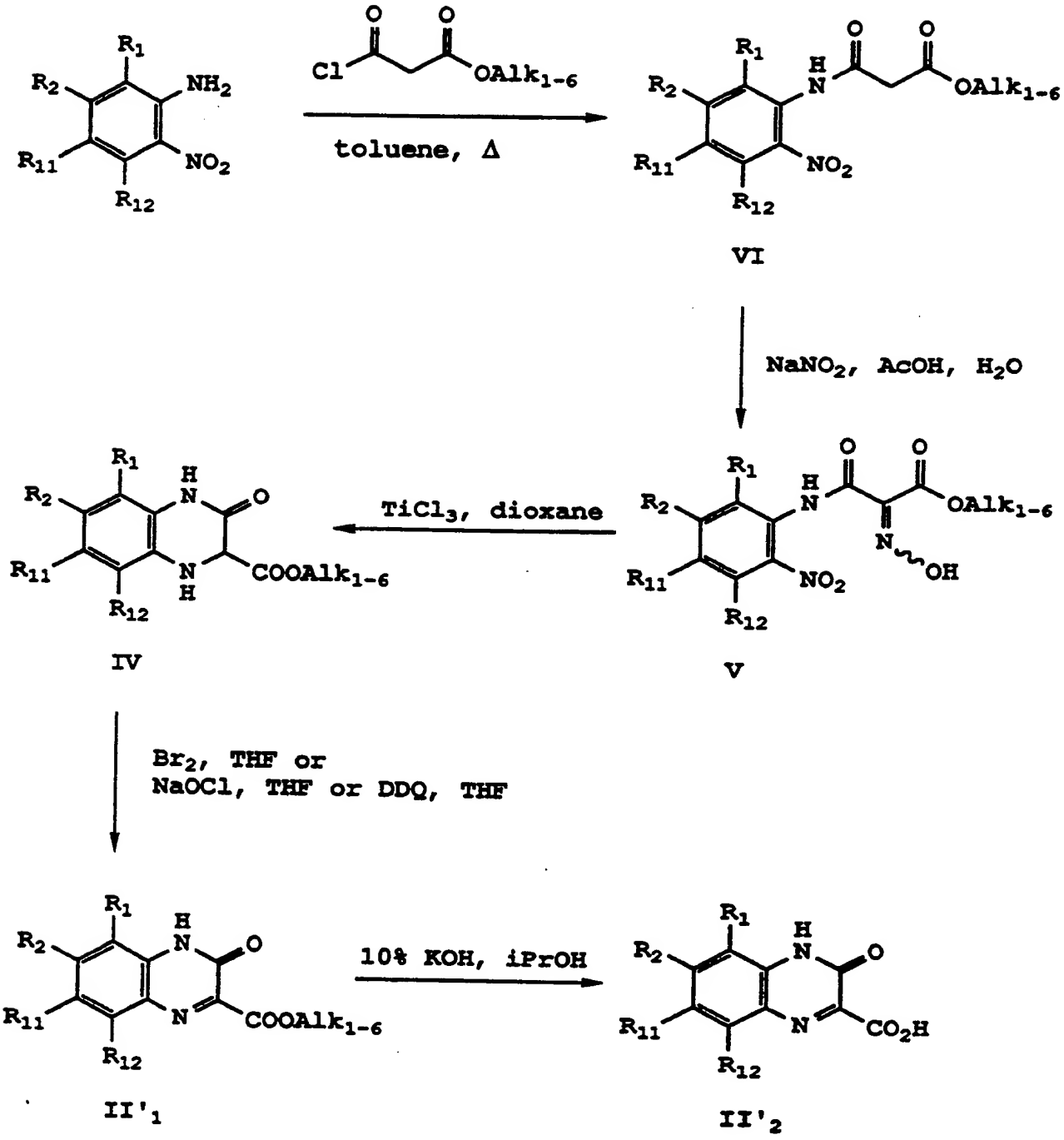
Scheme D consists of treating the compounds of Formula A with chloroethylmalonate, chloromethylmalonate, or the like in a solvent such as benzene or toluene or the like to provide the compounds of the Formula B. The compounds of the Formula B are then treated with sodium ethoxide in ethanol or sodium methoxide in methanol to provide the compounds of the Formula C. The compounds of the Formula C are further reacted with phosphorous trichloride or phosphorous tribromide in a solvent such as tetrahydrofuran, dioxane, or the like to provide the compounds of the Formula D.

Scheme D


R1
R2
NH2
R11
NO2
R12
A
Cl
O
O
OAlk1-6
toluene, Δ
B
NaOEt, EtOH, Δ
PCl3, THF, Δ
COOAlk1-6
C
D

Scheme E shows a preparation for compounds of the Formula I which consists of treating the compounds of the Formula VI with sodium nitrite, potassium nitrite, or the like in an acetic acid/tetrahydrofuran/water solvent mixture to provide the compounds of the Formula V. The compounds of the Formula V are then hydrogenated over Raney nickel in a solvent such as tetrahydrofuran or dioxane or the like, followed by treatment with aqueous titanium trichloride to provide the compounds of the Formula IV. The compounds of the Formula IV are further reacted with bromine, n-bromosuccinimide, NaOCl, or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to provide the compounds of the Formula II'_1. The compounds of the Formula II'_1 are subjected to saponification using KOH in water/iPrOH or the like to give the compounds of Formula II'_2.

Scheme E


toluene, Δ
VI
NaNO2, AcOH, H2O
TiCl3, dioxane
IV
V
Br2, THF or
NaOCl, THF or DDQ, THF
10% KOH, iPrOH
II'1
II'2

The preparation of Scheme E provides the preferred method of preparation for the Compound II'$_2$ defined above.

Generally, the compounds of the formula I above wherein X is $NHSO_2R^3$, NR^6R^3, NR^6OR^3, $NR^6CONR^3R^4$, NR^6COR^5, $NR^6CO_2R^3$, $NR^6NHSO_2R^3$, $NR^6NHCO_2R^3$, wherein R_1, R_2, R_{11}, R_{12}, R^3, R^4, R^5, and R^6 are as defined above, are prepared by the method of Schemes A-E above.

Scheme A consists of treating a carboxylic acid of the general structure (II) with a coupling reagent in an inert solvent to produce an activated carboxylic acid derivative. The resulting activated carboxylic acid derivative is reacted with a variety of nitrogen nucleophiles to produce amides of the general structures I', wherein X, R^1, R^2, R^3, R^4, R^5, and R^6 are as defined above. Suitable coupling agents for this purpose include, for example, such reagents as thionyl chloride, acetic anhydride, oxalyl chloride/ DMF, carbonyldiimidazole, DCC, and diphenylphosphoryl azide, preferably carbonyldiimidazole. By "activated carboxylic acid derivative" is meant an acid derivative which is capable of acylating an amine. Such acid derivatives include, for example, acid chlorides, acid bromides, anhydrides, and mixed anhydrides. By "inert solvent" is meant a nonprotic solvent such as, for example, methylene chloride, chloroform, carbon tetrachloride, ethyl acetate, tetrahydrofuran, and dimethylformamide.

Compounds of the Formula IIIa in Scheme C may be further reacted to protect the carbonyl of the quinoxaline ring with either a methoxy or allyloxy functionality to provide a compound of Formula IVa. The acid IVa is converted to the acid chloride followed by treatment with ammonia to produce the amide Va. Compounds of the Formula Va are further

elaborated by treatment with an isocyanate, symmetrical anhydride or a symmetrical pyrocarbonate to generate derivatives of structural Formula VIa. Formula VIa is deprotected with trimethylsilyl iodide or a combination of trimethylsilyl chloride and sodium iodide if the protecting ether is a methoxy group. The allyloxy group is removed using Wilkinson's catalyst to afford compounds of Formula VIIa.

Overall the compounds prepared in the Schemes A-E may optionally be further treated by conventional methods to obtain compounds of the Formula I wherein Y is S.

Pharmaceutically acceptable salts of the compounds of Formula I are also included as a part of the present invention.

The base salts may be generated from compounds of Formula I by reaction of the latter with one equivalent of a suitable nontoxic, pharmaceutically acceptable base followed by evaporation of the solvent employed for the reaction and recrystallization of the salt, if required. The compounds of Formula I may be recovered from the base salt by reaction of the salt with an aqueous solution of a suitable acid such as hydrobromic, hydrochloric, or acetic acid.

Suitable bases for forming base salts of the compounds of this invention include amines such as triethylamine or dibutylamine, or alkali metal bases and alkaline earth metal bases. Preferred alkali metal hydroxides and alkaline earth metal hydroxides as salt formers are the hydroxides of lithium, sodium, potassium, magnesium, or calcium. The class of bases suitable for the formation of nontoxic, pharmaceutically acceptable salts is well known to practitioners of the pharmaceutical formulation arts.

See, for example, Stephen N. Berge, et al, J. Pharm. Sci. 1977;66:1-19.

Suitable acids for forming acid salts of the compounds of this invention containing a basic group include, but are not necessarily limited to acetic, benzoic, benzenesulfonic, tartaric, hydrobromic, hydrochloric, citric, fumaric, gluconic, glucuronic, glutamic, lactic, malic, maleic, methanesulfonic, pamoic, salicylic, stearic, succinic, sulfuric, and tartaric acids. The acid addition salts are formed by procedures well known in the art.

Further, the compounds of this invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

Starting materials for the processes described above are known or can be prepared by known processes.

The products of the reactions described herein are isolated by conventional means such as extraction, crystallization, distillation, chromatography, and the like.

PHARMACEUTICAL COMPOSITIONS

The compounds of the present invention can be administered in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component, either a compound of Formula I or a corresponding pharmaceutically acceptable salt of a compound of Formula I.

For preparing pharmaceutical compositions from the compounds of the present invention,

pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The

molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents, as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or

ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 1 mg to 1000 mg preferably 10 mg to 100 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

METHOD OF TREATING

The compounds of this invention are extremely useful in the treatment of central nervous system disorders related to their biological activity. The compounds of this invention may accordingly be administered to a subject, including a human, in need of treatment, alleviation, or elimination of an indication associated with the biological activity of the compounds. This includes especially excitatory amino acid dependent psychosis, excitatory amino acid dependent anorexia, excitatory amino acid dependent ischemia, excitatory amino acid dependent convulsions, and excitatory amino acid dependent migraine. Suitable dosage ranges are 0.1 to 1000 mg daily, 10 to 400 mg daily, and especially 30 to 100 mg daily, dependent as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and further, the preference and experience of the physician or veterinarian in charge.

The following nonlimiting examples illustrate the present invention.

General Preparation 1

Preparation of Selected Acylsulphonamides

Solution A: 14.1 g, 0.087 mole carbonyldiimidazole is dissolved in 250 mL dry DMF. To this is added 0.029 mole of a suitably substituted 2-oxo-quinoxoline-3-carboxylate. This solution is heated at 80°C for 2 hours under nitrogen, then dry DMF to make 300 mL is added and the solution cooled to 25°C.

Solution B: To a suspension of 0.38 g, 0.0116 mole sodium hydride in 30 mL dry DMF is added in one portion 0.0116 mole of the selected sulphonamide. This is stirred at 25°C for 2 hours.

To Solution B is added 60 mL of Solution A at once. A solid is formed at this point. In the cases where the solid rapidly went into solution the reaction is stirred at 25°C for 1 to 5 days. When a solid remained after the mixing of the solutions, the reaction is refluxed for 1 to 8 hours to go to completion.

In either case, the reaction is worked up by pouring into a mixture of 300 g each of ice and concentrated HCl. The precipitated solid is washed with water. The crude product is dissolved in hot DMF and precipitated with the addition of water. After cooling the solid is filtered, washed with cold DMF, water, heptane, then dried for 24 hours at 140°C under vacuum to yield the product as a yellow powder. In some cases acetonitrile, diethyl ether, or methanol is substituted for DMF as the washing solvent.

General Preparation 2
Preparation of 3,4-dihydro-N-alkoxy-3-oxo-2-quinoxaline carboxamides

Solution B: To a suspension of 0.38 g, 0.0116 mole sodium hydride in 30 mL anhydrous DMF is added in one portion 0.0116 mole of the selected O-alkylhydroxylamine hydrochloride or O-alkylaryl-hydroxylamine hydrochloride. This is stirred at 25°C for 1 hour.

To Solution B is added 60 mL of Solution A as described for Method A. The reaction is stirred at 25°C for 1 to 5 days. The reaction is poured into a mixture of 300 g each of ice and 3N HCl. The solid is washed with 50 mL 5% $NaHCO_3$, 50 mL water, 50 mL acetonitrile, and 50 mL diethylether. The product is dried at 140°C under vacuum. In some cases the product is recrystallized from DMF/water or is triturated by washing with hot acetonitrile or ethanol.

General Preparation 3
Preparation of 3,4-dihydro-N-alkyl-3-oxo-2-quinoxaline carboxamides

Solution B: To a suspension of 0.38 g, 0.0116 mole sodium hydride in 20 mL anhydrous DMF is added in one portion 0.116 mole of the selected amine hydrochloride of alternatively the free base of the amine may be employed directly without the use of sodium hydride.

To Solution B is added 60 mL of Solution A as described for Method A. The reaction is stirred at 25°C for 1 to 5 days or stirred at 25°C for 18 hours and then heated to 80°C for 1 to 4 hours. The reaction is poured into a mixture of 300 g each of ice and 3N HCl. The solid is washed with 50 mL 5% $NaHCO_3$,

50 mL water, 50 mL acetonitrile, and 50 mL diethylether. The product is dried at 140°C under vacuum. In some cases the product is recrystallized from DMF/water or is triturated by washing with hot acetonitrile or ethanol.

General Preparation 4
Preparation of 3,4-dihydro-3-oxo-N-[[(alkyl)amino]-carbonyl]-2-quinoxalinecarboxamides

To 60 mL of Solution A in Method A is added 1.49 g, 0.023 mol of sodium cyanate. The reaction is stirred at 25°C for 18 hours. The solvent is removed in vacuo at 60°C. Chloroform is added and the crude beige solid was filtered. The solid is slurried in 140 mL of anhydrous DMF and at least 0.046 mole of an alkyl or alkylaryl amine is added and the reaction was heated to 60°C for 18 hours. The reaction is poured into a mixture of 300 g each of ice and 3N HCl. The solid is washed with 50 mL 5% $NaHCO_3$, 50 mL water, 50 mL acetonitrile, and 50 mL diethylether. The product is purified on a silica gel column eluted initially with methylene chloride followed by methanol/methylene chloride up to 30% methanol. The chromatographed product is washed with hot acetonitrile and filtered. The product is dried at 140°C under vacuum.

General Preparation 5
Preparation of 3,4-dihydro-3-[(alkoxy)carbonyl]-2-quinoxaline carboxamides

To 60 mL of Solution A is described in Method A is added 1.49 g, 0.023 mol of sodium cyanate. The reaction is stirred at 25°C for 18 hours. The solvent is removed in vacuo at 60°C. Chloroform is added and the crude beige solid was filtered. The solid is

slurried in 140 mL of anhydrous DMF and at least 0.046 mole of an alcohol is added and the reaction is heated to 60°C for 18 hours. The reaction is poured into a mixture of 300 g each of ice and 3N HCl. The solid is washed with 50 mL 5% $NaHCO_3$, 50 mL water, 50 mL acetonitrile, and 50 mL diethylether. The product is purified on a silica gel column eluted initially with methylene chloride followed by methanol/methylene chloride up to 30% methanol. The chromatographed product is washed with hot acetonitrile and filtered. The product is dried at 140°C under vacuum.

EXAMPLE 1

6,7-Dichloro-3,4-dihydro-3-oxo-N-[(phenyl)sulfonyl]-2-quinoxalinecarboxamide

A solution containing benzenesulphonamide (0.91 g, 5.8 mmol) and sodium hydride (0.24 g, 5.79 mmol) in dry DMF (10 mL) was heated to 60°C for 2 hours and cooled. A solution containing 3.9 mmol of the reagent prepared as described in General Preparation 1, Solution A was added to the benzenesulfonamide mixture. The reaction was stirred at 25°C for 18 hours, poured onto ice/HCl and the precipitate was collected and dried to produce the amide as a yellow solid (0.7 g, 90% yield); mp 325-330°C.

Elemental analysis calculated for $C_{13}H_{14}Cl_2N_4O_2$:

C, 45.24; H, 2.28; N, 10.55; Cl, 17.80; S, 8.05.

Found: C, 44.90; H, 1.94; N, 10.46; Cl, 17.90; S, 8.24.

EXAMPLE 2

6,7-Dichloro-N-[2-(dimethylamino)ethyl]-3,4-dihydro-3-oxo-2-quinoxalinecarboxamide

To a solution containing N,N'-dimethylethylenediamine (1.02 g, 11.6 mol) was in dry DMF (20 mL) was added a solution containing 5.8 mmol of the reagent prepared as described in General Preparation 1, Solution A. A yellow precipitate formed within 5 minutes and the reaction was stirred an additional 16 hours at 25°C. The reaction was poured onto ice and the precipitate was collected and dried to produce the amide as a yellow solid (1.38 g, 72% yield); m.p. 272-274°C.

Elemental analysis calculated for $C_{13}H_{14}Cl_2N_4O_2$:

C, 47.41; H, 4.20; N, 17.10.

Found: C, 47.43; H, 4.29; N, 17.02.

EXAMPLE 3

6,7-Dichloro-3,4-dihydro-3-oxo-N-(phenylmethoxy)-2-quinoxalinecarboxamide

Sodium hydride (2.49 g, 15.6 mmol) was suspended in anhydrous DMF (20 mL) and O-benzylhydroxyamine hydrochloride (2.49 g, 15.6 mmol) was added in one batch. The reaction was stirred for 1 hour and a solution containing 7.7 mmol of the reagent prepared as described in General Preparation 1, Solution A was added. The reaction was stirred at 25°C for 4 days. The reaction was poured onto ice containing 6 N HCl and a yellow solid precipitated. The solid was filtered and washed with water followed by hot acetonitrile to produce the hydroxamate (2.23 g, 79% yield); m.p. 279-280°C.

Elemental analysis calculated for $C_{16}H_{11}Cl_2N_3O_3$:

C, 52.77; H, 3.04; N, 11.54.

Found: C, 52.51; H, 2.97; N, 11.73.

EXAMPLE 4

N-(Aminocarbonyl)-6,7-dichloro-3,4-dihydro-3-oxo-2-quinoxalinecarboxamide

4,5-Dichloro-1,2-phenylenediamine (8.0 g, 45.2 mmol) was dissolved in ethanol (300 mL) and water (30 mL). Alloxan monohydrate (7.24 g, 45.2 mmol) was dissolved in ethanol/water (30 mL:70 mL) and added dropwise to the diamine solution. The reaction was stirred for 20 hours and the precipitate was collected by filtration. This crude product was slurried in hot DMF (steam bath) and filtered. The solid was washed with water, acetonitrile, and diethylether to produce the title compound as a yellow solid (10.5 g, 77% yield); m.p. >300°C.

Elemental analysis calculated for $C_{10}H_6Cl_2N_4O_3$:
C, 39.89; H, 2.01; N, 18.61; Cl, 23.55.
Found: C, 39.75; H, 1.87; N, 18.52; Cl, 23.64.

EXAMPLE 5

6,7-Dichloro-3,4-dihydro-3-oxo-N-[[(phenylmethyl)-amino]carbonyl]-2-quinoxalinecarboxamide

Sodium cyanate (1.0 g, 15.3 mmol) was added to a solution containing 3.35 mmol of the reagent prepared as described in General Preparation 1, Solution A. The Reaction was stirred at 25°C for 18 hours. The solvent was removed in vacuo at 60°C and the solid

liquor was further acidified to pH 2 and the yellow solid was filtered to produce a crude product (0.70 g) containing the title compound as the major component. This second solid was crystallized from DMF/water to afford the product as an off-white solid (0.67 g, 44% yield); m.p. 292-295°C.

Elemental analysis calculated for $C_{17}H_{12}Cl_2N_4O_3$:
C, 52.19; H, 3.09; N, 14.32; Cl, 18.12.
Found: C, 52.12; H, 3.27; N, 14.14; Cl, 18.03.

EXAMPLE 6

6,7-Dichloro-3,4-dihydro-3-oxo-N-[(phenylamino)-carbonyl]-2-quinoxalinecarboxamide

Step 1

Ethyl-3,6,7-trichloro-2-quinoxalinecarboxylate

Ethyl-6,7-dichloro-3,4-dihydro-3-oxo-2-quinoxalinecarboxylate (36.0 g, 0.125 mol) was suspended in toluene (500 mL) and DMF (12.5 mL) and thionyl chloride (12.5 mL, 0.17 mol) were added. The reaction was heated to reflux for 2 hours and the solution turned a deep purple. The reaction was cooled and the toluene was removed under reduced pressure. The crude material was chromatographed on a silica gel plug eluted with methylene chloride. The title compound was isolated as a pink solid (35.5 g, 93% yield). An analytical sample was prepared by recrystallization from hexane; m.p. 102-104°C.

Elemental analysis calculated for $C_{11}H_7Cl_3N_2O_2$:
C, 43.24; H, 2.31; N, 9.17.
Found: C, 43.28; H, 2.23; N, 8.89.

Step 2

6,7-Dichloro-3-methoxy-2-quinoxalinecarboxylate

Sodium metal was added in small pieces to anhydrous MeOH (1500 mL) and the resulting sodium

methoxide solution was cooled to 25°C. Ethyl-3,6,7-trichloro-2-quinoxalinecarboxylate (36.4 g, 0.119 mol) was added and the reaction was stirred for 18 hours. Water (500 mL) was added and the reaction was stirred for 3 hours at 25°C. The solvent was concentrated under reduced pressure to one-third of its original volume and the slurry was acidified to pH 2 with 25% hydrochloric acid. The mixture was stirred 30 minutes and the solid was filtered to yield the acid as a gray solid (30.8 g, 95% yield); m.p. 181-182°C.

Elemental analysis calculated for $C_{10}H_6Cl_2N_2O_3$:
C, 43.98; H, 2.21; N, 10.26.
Found: C, 43.92; H, 2.02; N, 10.24.

Step 3

<u>6,7-Dichloro-3-methoxy-2-quinoxalinecarboxamide</u>

6,7-Dichloro-3-methoxy-2-quinoxalinecarboxylate (16.38 g, 0.06 mol) was suspended in methylene chloride and oxalyl chloride (6.24 mL, 0.072 mol) and DMF (2 drops) was added. The reaction was stirred for 18 hours and the methylene chloride was removed under reduced pressure. The crude acid chloride was dissolved in anhydrous THF (500 mL) and ammonia gas was bubbled through the reaction for 1 hour. The reaction was then stirred for 18 hours at 25°C. The reaction was poured into water and the precipitate was collected by filtration to afford the amide as an off-white solid (14.41 g, 88% yield); m.p. 237-241°C.

Elemental analysis calculated for $C_{10}H_7Cl_2N_3O_2$:
C, 44.14; H, 2.59; N, 15.44.
Found: C, 44.07; H, 2.60; N, 15.33.

Step 4

6,7-Dichloro-3-methoxy-N-[(phenylamino)carbonyl]-2-quinoxalinecarboxamide

6,7-Dichloro-3-methoxy-2-quinoxalinecarboxamide (1.75 g, 0.0064 mol) was dissolved in toluene (500 mL) and phenyl isocyanate (1.19 g, 0.01 mol) was added. The reaction was refluxed for 24 hours and the toluene layer was extracted with water, dried ($MgSO_4$), filtered, and concentrated. The crude product was chromatographed on silica gel eluted with CH_2Cl_2/MeOH (95:5) to produce the acyl urea (1.44 g, 58% yield). A sample was recrystallized from CH_2Cl_2/THF to afford an analytical sample.

Elemental analysis calculated for $C_{17}H_{12}Cl_2N_4O_3$:

C, 52.19; H, 3.09; N, 14.32.

Found: C, 52.10; H, 2.79; N, 14.16.

Step 5

6,7-Dichloro-3,4-dihydro-3-oxo-N-[(phenylamino)-carbonyl]-2-quinoxalinecarboxamide

6,7-Dichloro-3-methoxy-N-[(phenylamino)carbonyl]-2-quinoxalinecarboxamide (1.25 g, 0.0032 mol) was dissolved in methylene chloride (200 mL) and trimethylsilyl iodide was added. The reaction was stirred at 25°C for 18 hours. The reaction was poured into 5% sodium bisulfite and stirred for 10 minutes. The two layers were filtered to produce a crude solid. The solid was dissolved in a minimum of DMF, stirred over charcoal and filtered through a Celite pad. The bright yellow solution was diluted with EtOH so that the composition of the solution was approximately EtOH/DMF (2:1). Water was added to the point of cloudiness, the solution was cooled to 5°C and filtered to produce the title compound as a yellow solid (0.21 g, 17% yield); m.p. >300°C.

Elemental analysis calculated for $C_{16}H_{10}Cl_2N_4O_3$:
C, 50.95; H, 2.67; N, 14.85.
Found: C, 50.73; H, 2.56; N, 14.83.

EXAMPLE 7

N-acetyl-6,7-dichloro-3,4-dihydro-3-oxo-2-quinoxaline-carboxamide

Step 1

6,7-Dichloro-3(2-propenyloxy)-2-quinolinecarboxylic acid

Sodium metal (2.8 g, 0.122 mol) was added in small pieces to allyl alcohol (150 mL) over a 20-minute period. The allyloxy solution was cooled to 25°C and ethyl-3,6,7-trichloro-2-quinoxaline-carboxylate was added in one batch. The solid dissolved in solution briefly and a precipitate then formed. The reaction was stirred at 25°C for 18 hours and water (60 mL) was added and the reaction was stirred for an additional 4 hours. The allyl alcohol was removed under reduced pressure and water (100 mL) was added. The reaction was acidified to pH 2 with 6N hydrochloric acid. A precipitate formed and was filtered and washed with water to afford the title compound as a pale purple solid (6.58 g, 85% yield); m.p. 160-161°C.

Elemental analysis calculated for $C_{12}H_8Cl_2N_2O_3 \cdot 0.15H_2O$:
C, 47.76; H, 2.77; N, 2.98.
Found: C, 45.57; H, 2.77; N, 9.11.

Step 2

6,7-Dichloro-3-(2-propenyloxy)-2-quinoxaline-carboxamide

6,7-Dichloro-3-[(1-propyl-2-ene)oxy]-2-quinoxalinecarboxylate (5.0 g, 0.0167 mol) was suspended in methylene chloride and oxalyl chloride

(1.75 mL, 0.02 mol) and DMF (2 drops) was added. The reaction was stirred for 4 hours and the methylene chloride was removed under reduced pressure. The crude acid chloride was dissolved in anhydrous THF (150 mL) and ammonia gas was bubbled through the reaction for 30 minutes. The reaction was then stirred for 18 hours at 25°C. The reaction was poured into water and the precipitate was collected by filtration to afford the amide as an off-white solid (4.57 g, 95% yield); m.p. 185-186°C.

Elemental analysis calculated for $C_{12}H_9Cl_2N_3O_2$:
C, 52.96; H, 4.44; N, 12.35.
Found: C, 51.53; H, 4.26; N, 12.04.

Step 3

Ethyl [[6,7-dichloro-3-(2-propenyloxy)-2-quinoxalinyl]carbonyl]carbamate

Dichloro-3-(2-propenyloxy)-2-quinoxaline-carboxamide (0.5 g, 1.68 mmol) and diethyl-pyrocarbonate (20 mL) were heated at 140°C for 18 hours. The carbonate was removed under reduced pressure and the crude product was chromatographed on a silica gel column eluted with methylene chloride. The product eluted as a clear oil which solidified upon standing (0.32 g, 51% yield).

Step 4

Ethyl [[6,7-dichloro-3,4-dihydro-3-oxo-2-quinoxalinyl]carbonyl]carbamate

6,7-Dichloro-3-[(1-propyl-2-ene)oxy]-N-(ethoxy-carbonyl)-2-quinoxalinecarboxamide (0.32 g, 0.97 mmol) was dissolved in THF (18 mL) and water (2 mL) and tris(triphenylphosphine)rhodium chloride (30 mg). The reaction was refluxed for 30 minutes, cooled, and filtered through a Celite pad. The THF was removed under reduced pressure and the crude product was

recrystallized from ethyl acetate to afford the title compound as a yellow solid (80 mg).

EXAMPLE 8

N-acetyl-6,7-dichloro-3,4-dihydro-3-oxo-2-quinoxaline-carboxamide

Step 1

N-acetyl-6,7-dichloro-3-(2-propenyloxy)-2-quinoxaline-carboxamide

6,7-Dichloro-3-(2-propenyloxy)-2-quinoxaline-carboxamide (1.2 g, 0.004 mol) was suspended in acetic anhydride and heated to reflux for 18 hours. The reaction was cooled and the acetic anhydride was removed under reduced pressure at 60°C. The crude solid was recrystallized from toluene to yield the imide as a beige solid (0.58 g, 43% yield).

Elemental analysis calculated for $C_{14}H_{10}Cl_2N_3O_3$:

C, 49.58; H, 2.97; N, 12.39.

Found: C, 49.32; H, 3.19; N, 12.29.

Step 2

N-acetyl-6,7-dichloro-3,4-dihydro-3-oxo-2-quinoxaline-carboxamide

N-acetyl-6,7-dichloro-3-(2-propenyloxy)-2-quinoxalinecarboxamide (0.50 g, 1.47 mmol) was dissolved in EtOH (18 mL) and water (2 mL) and tris(triphenylphosphine)rhodium chloride (50 mg). The reaction was refluxed for 30 minutes and a yellow solid precipitated out and filtered from the reaction while it was hot. The solid was crystallized from DMF/water to produce the title compound as a bright yellow solid (0.22 g, 39% yield); m.p. 297-300°C (dec).

Elemental analysis calculated for $C_{11}H_7Cl_2N_3O_3$:
C, 44.03; H, 2.35; N, 14.00.
Found: C, 43.76; H, 2.32; N, 13.85.

EXAMPLE 9

6,7-Dichloro-3,4-dihydro-3-oxo-2-(methoxycarbonyl)-hydrazide-2-quinoxalinecarboxylic acid

To a solution of methylcarbazate (3.5 g, 38.6 mmol) in dry DMF (50 mL) is added a solution containing 7.72 mol of the reagent prepared as described in General Preparation 1, Solution A. The reaction is stirred at 25°C for 4 days and poured into water (500 mL). The solution is made acidic with 6N HCl to pH 2. The precipitate is collected and taken up in hot DMF. The DMF solution is treated with charcoal and filtered. The solution is cooled and diluted with an equal volume of water. The yellow solid is collected by filtration and is washed with acetonitrile followed by diethylether to afford the title compound (2.56 g, 100% yield); m.p. 333-340°C (decomposes).

Elemental analysis calculated for $C_{11}H_8N_4O_4Cl_2$:
C, 39.9; H, 2.44; N, 16.92; Cl, 21.41.
Found: C, 39.52; H, 2.29; N, 16.86; Cl, 21.94.

EXAMPLE 10

6,7-Dichloro-3,4-dihydro-3-oxo-2-(phenylsulfonyl)-hydrazide-2-quinoxalinecarboxylic acid

Solution B: To a suspension of sodium hydride (1.5 g, 38.6 mmol) (60% dispersion in mineral oil) in dry DMF (20 mL) is added benzenesulfonylhydrazide (6.65 g, 38.6 mmol). The reaction is stirred at 25°C for 1 hour and a solution containing 7.72 mmol of the reagent prepared as described in General Preparation 1, Solution A is added to Solution B.

This solution is stirred at 90°C for 24 hours and then is poured into water (500 mL). The solution is made acidic with 6N HCl to pH 2. The solid is collected and recrystallized twice from hot DMF/water, washed with acetonitrile, followed by diethylether, and then dried at 137°C under vacuum to give the title compound (1.44 g, 45% yield) as a yellow solid; m.p. 283°C.

Elemental analysis calculated for $C_{15}H_{10}N_4O_4Cl_2S$:
C, 43.6; H, 2.44; N, 13.56; Cl, 17.16.
Found: C, 43.23; H, 2.26; N, 13.80; Cl, 17.69.

EXAMPLE 11

N-Benzoyl-6,7-dichloro-3,4-dihydro-3-oxo-2-quinoxalinecarboxamide

Solution B: To a suspension of sodium hydride (0.93 g, 23.2 mmol) (60% dispersion in mineral oil) in dry DMF (20 mL) is added benzamide (2.81 g, 23.2 mmol). The solution is stirred at 25°C for 1 hour. A solution containing 7.72 mmol of the reagent prepared as described in General Preparation 1, Solution A is added to Solution B. The reaction is stirred at 25°C for 24 hours and the solution is poured into water (500 mL). The solution is made acidic with 6N HCl to pH 2. The solid is collected and taken up in hot DMF. The DMF solution is treated with charcoal and filtered. The solution is cooled and diluted with an equal volume of water. The yellow solid is collected, washed with acetonitrile followed by diethylether to give the title compound (1.09 g, 39% yield) as a yellow solid; m.p. 302°C (decomposes).

Elemental analysis calculated for $C_{16}H_9N_3O_3Cl_2$:
C, 53.06; H, 2.5; N, 11.6; Cl, 19.58.
Found: C, 52.65; H, 2.28; N, 11.79; Cl, 19.78.

EXAMPLE 12

6,7-Dichloro-3-hydroxy-N-(1-piperidinylcarbonyl)-2-quinoxalinecarboxamide

Solution B: To a suspension of sodium hydride (0.93 g, 23.2 mmol) (60% dispersion in mineral oil) in dry DMF (20 mL) is added 1-piperidinecarboxamide (2.97 g, 23.2 mmol). The solution is stirred at 60°C for 0.5 hours. A solution containing 0.00772 mol of the reagent prepared as described in General Preparation 1, Solution A is added to Solution B. This is stirred as 60°C for 3 days. The solution is poured into water (500 mL) and the solution is made acidic with 6N HCl to pH 2. The solid is collected and taken up in hot DMF. The DMF solution is treated with charcoal and filtered. The solution is cooled and diluted with an equal volume of water. The yellow solid is collected, washed with acetonitrile followed by diethylether to give the title compound (0.95 g, 33% yield) as a yellow solid; m.p. 277-278°C.

Elemental analysis calculated for $C_{15}H_{14}N_4O_3Cl_2$:

acidic with 6N HCl to pH 2. The solid is collected and taken up in hot DMF. The DMF solution is treated with charcoal and filtered. The solution is cooled and diluted with an equal volume of water. The yellow solid is collected, washed with acetonitrile followed by diethylether to afford the title compound (1.5 g, 59% yield) as a yellow solid; m.p. 289-90°C.
Elemental analysis calculated for $C_{12}H_{10}N_4O_3Cl_2$:
C, 43.79; H, 3.06; N, 17.02; Cl, 21.54.
Found: C, 43.76; H, 3.03; N, 16.95; Cl, 21.60.

Likewise, in a manner analogous to the procedures of General Preparations 1-3, but using appropriate corresponding starting materials the following compounds were prepared.

EXAMPLE 14

α-[[(6,7-Dichloro-3,4-dihydro-3-oxo-2-quinoxalinyl]-carbonyl]amino-(±)-benzeneacetic acid; 9.8% yield, m.p. 244-252°C (dec.)
Calcd.: C, 52.06; H, 2.83; N, 10.71.
Found: C, 51.98; H, 2.89; N, 10.85.

EXAMPLE 15

6,7-Dichloro-3,4-dihydro-N-(methylsulfonyl)-3-oxo-2-quinoxalinecarboxamide; 32% yield; m.p. >355°C.
Calcd: C, 35.73; H, 2.10; N, 12.50.
Found: C, 35.74; H, 2.02; N, 12.27.

EXAMPLE 16

6,7-Dichloro-3,4-dihydro-N-hydroxy-3-oxo-2-quinoxalinecarboxamide; 44% yield; m.p. >300°C.
Calcd: C, 39.44; H, 1.84; N, 15.33.
Found: C, 39.22; H, 1.59; N, 14.95.

EXAMPLE 17

N-(Butylsulfonyl)-6,7-dichloro-3,4-dihydro-3-oxo-2-quinoxalinecarboxamide; m.p. >295°C.

Calcd: C, 41.28; H, 3.46; N, 11.11.

Found: C, 41.22; H, 3.22; N, 11.22.

EXAMPLE 18

6,7-Dichloro-3,4-dihydro-N-methyl-3-oxo-2-quinoxalinecarboxamide; 95% yield; m.p. >300°C.

Calcd: C, 44.14; H, 2.59; N, 15.44.

Found: C, 43.83; H, 2.67; N, 15.10.

EXAMPLE 19

6,7-Dichloro-3,4-dihydro-N-methoxy-3-oxo-2-quinoxalinecarboxamide; 67% yield; m.p. 298-300°C.

Calcd: C, 41.69; H, 2.45; N, 14.59.

Found: C, 41.66; H, 2.37; N, 14.22.

EXAMPLE 20

6,7-Dichloro-3,4-dihydro-3-oxo-2-quinoxalinecarboxamide; 94% yield; m.p. >320°C.

Calcd: C, 41.89; H, 1.95; N, 16.28.

Found: C, 41.62; H, 1.63; N, 16.06.

EXAMPLE 21

6,7-Dichloro-3,4-dihydro-3-oxo-N-(phenylmethyl)-2-quinoxalinecarboxamide; 86% yield; m.p. >320°C.

Calcd: C, 55.19; H, 3.18; N, 12.07.

Found: C, 54.97; H, 3.18; N, 11.96.

EXAMPLE 22

1-[(6,7-Dichloro-3,4-dihydro-3-oxo-2-quinoxalinyl)-carbonyl]-4-(phenylmethyl-piperazine monohydrochloride; m.p. >290°C (dec).

Calcd: C, 52.94; H, 4.22; N, 12.35.

Found: C, 52.59; H, 4.40; N, 12.45.

EXAMPLE 23

[[(6,7-Dichloro-3,4-dihydro-3-oxo-2-quinoxalinyl)-carbonyl]amino acetic acid, 1,1-dimethylethyl ester; 74% yield; m.p. >300°C.

Calcd (with 0.25 H_2O):

C, 47.83; H, 4.15; N, 11.16; Cl, 18.82.

Found: C, 47.65; H, 4.05; N, 11.18; Cl, 18.84.

EXAMPLE 24

N-[(6,7-Dichloro-3,4-dihydro-3-oxo-2-quinoxalinyl)-carbonyl]glycine; 98% yield; m.p. 285-306°C (dec).

Calcd: C, 41.80; H, 2.23; N, 13.29.

Found: C, 41.52; H, 2.04; N, 13.14.

EXAMPLE 25

[[[(6,7-Dichloro-3,4-dihydro-3-oxo-2-quinoxalinyl)-carbonyl]amino]acetic acid; 62% yield; m.p. 248-268°C (dec).

Calcd: C, 39.78; H, 2.12; N, 12.65.

Found: C, 39.71; H, 2.17; N, 13.09.

EXAMPLE 26

6,7-Dichloro-3,4-dihydro-N-[(4-methylphenyl)sulfonyl]-3-oxo-2-quinoxalinecarboxamide; 43% yield; m.p. 320°C.

Calcd: C, 46.62; H, 2.69; N, 10.19; Cl, 17.20; S, 7.78.

Found: C, 46.47; H, 2.61; N, 10.08; Cl, 17.33; S, 7.66.

EXAMPLE 27

6,7-Dichloro-3,4-dihydro-N-[(2-chloro-5-nitrophenyl)-sulfonyl]-3-oxo-2-quinoxalinecarboxamide; 81% yield; m.p. 340°C.

Calcd: C, 37.72; H, 1.48; N, 11.73; Cl, 22.27; S, 6.71.

Found: C, 38.10; H, 1.52; N, 11.66; Cl, 22.01; S, 7.01.

EXAMPLE 28

6,7-Dichloro-N-[(4-chloro-2-nitrophenyl)sulfonyl]-3,4-dihydro-3-oxo-2-quinoxalinecarboxamide; 93% yield; m.p. 330°C.

Calcd: C, 37.72; H, 1.48; N, 11.73; Cl, 22.27; S, 6.71.

Found: C, 37.61; H, 1.28; N, 11.53; Cl, 22.27; S, 7.19.

PREPARATION 1

3,4-Dihydro-7-nitro-3-oxo-2-quinoxalinecarboxylic acid

3-Hydroxy-2-quinoxaline carboxylic acid (10.0 g, 52.6 mmole) was dissolved in concentrated H_2SO_4 (150 mL), and cooled in an ice bath. Powdered potassium nitrate (16.0 g, 178 mmole), was added in portions with stirring, and the reaction was allowed to warm overnight. In the morning the reaction was poured onto 600 g ice and when the ice melted the precipitate was filtered. The solid was dissolved in boiling water (1600 mL), hot filtered, and then cooled and the precipitate filtered to give (7.5 g, 64%) of the title compound. Recrystallization from ethanol/water afforded 3,4-dihydro-7-nitro-3-oxo-2-quinoxalinecarboxylic acid as a yellow solid.

Elemental analysis calculated for 2 mole H_2O:
C; 39.89; H, 3.34; N, 15.51.
Found: C, 39.89; H, 3.37; N, 15.30.

Preparations 2 and 3 are analogous to those of U.S. Patent 4,264,600 beginning with corresponding appropriate starting materials.

PREPARATION 2

Ethyl-6-nitro-3,4-dihydro-3-oxo-quinoxaline-2-carboxylate; 52% yield; m.p. 229°C.
Calcd: C, 50.16; H, 3.48; N, 15.78.
Found: C, 50.20; H, 3.45; N, 15.96.

PREPARATION 3

6-Nitro-3,4-dihydro-3-oxo-quinoxaline-2-carboxylic acid; 75% yield; m.p. 270°C.
Calcd: C, 45.97; H, 2.14; N, 17.87.
Found: C, 45.82; H, 2.10; N, 17.75.

EXAMPLE 29

6,7-Dichloro-3,4-dihydro-N-(2-thionylsulfonyl)-3-oxo-2-quinoxalinecarboxamide; 22% yield; m.p. 320°C.
Calcd: C, 38.63; H, 1.25; N, 10.39; Cl, 17.54.
Found: C, 38.75; H, 1.58; N, 10.29; Cl, 17.71.

EXAMPLE 30

6,7-Dichloro-3,4-dihydro-N-[(4-methoxyphenyl)-sulfonyl]-3-oxo-2-quinoxalinecarboxamide; 45% yield; m.p. 313°C.
Calcd: C, 44.87; H, 2.59; N, 9.81; Cl, 16.56; S, 7.49.
Found: C, 44.75; H, 2.65; N, 9.74; Cl, 16.46; S, 7.72.

EXAMPLE 31

6,7-Dichloro-3,4-dihydro-N-[(4-bromophenyl)sulfonyl]-3-oxo-2-quinoxalinecarboxamide; 25% yield; m.p. 330°C.

Calcd: C, 37.76; H, 1.69; N, 8.81; Cl, 14.86; Br, 16.75.

Found: C, 38.93; H, 1.90; N, 8.42; Cl, 14.76; Br, 17.03.

EXAMPLE 32

6,7-Dichloro-3,4-dihydro-N-[(2-methylphenyl)sulfonyl]-3-oxo-2-quinoxalinecarboxamide; 21% yield; m.p. 322°C.

Calcd: C, 46.62; H, 2.69; N, 10.19; Cl, 17.20; S, 7.78.

Found: C, 46.66; H, 2.63; N, 10.12; Cl, 17.28; S, 7.72.

EXAMPLE 33

6,7-Dichloro-3,4-dihydro-N-[(4-chlorophenyl)sulfonyl]-3-oxo-2-quinoxalinecarboxamide; 12% yield; m.p. 335°C.

Calcd: C, 41.64; H, 1.86; N, 9.71.

Found: C, 41.41; H, 1.96; N, 9.62.

EXAMPLE 34

6,7-Dichloro-3,4-dihydro-3-oxo-N-[[5-(2-pyridinyl)-2-thienyl]sulfonyl]-2-quinoxalinecarboxamide; 52% yield; m.p. 325°C.

Calcd: C, 44.92; H, 2.09; N, 11.64.

Found: C, 45.49; H, 2.03; N, 11.21.

EXAMPLE 35

6,7-Dichloro-3,4-dihydro-3-oxo-N-[[3-(trifluoromethyl)phenyl]sulfonyl]-2-quinoxalinecarboxamide; 25% yield; m.p. 310-312°C.

Calcd: C, 41.22; H, 1.73; N, 9.01; Cl, 15.21; F, 12.22; S, 6.89.

Found: C, 41.10; H, 1.43; N, 9.12; Cl, 15.55; F, 18.82; S, 6.55.

EXAMPLE 36

6,7-Dichloro-3,4-dihydro-3-oxo-N-[(4-fluorophenyl)-sulfonyl]-2-quinoxalinecarboxamide; 33% yield; m.p. 313-315°C.

Calcd: C, 43.29; H, 1.94; N, 10.10; Cl, 17.04; F, 4.56; S, 7.70.

Found: C, 43.07; H, 2.01; N, 9.97; Cl, 17.02; F, 7.40; S, 7.70.

EXAMPLE 37

6,7-Dichloro-N-[(2,3-dihydro-(H-inden-5-yl)sulfonyl]-3,4-dihydro-3-oxo-2-quinoxalinecarboxamide; 22% yield; m.p. 320-322°C.

Calcd: C, 49.33; H, 2.99; N, 9.59; Cl, 16.18; S, 7.32.

Found: C, 49.46; H, 2.94; N, 9.68; Cl, 16.95; S, 7.31.

EXAMPLE 38

6,7-Dichloro-3,4-dihydro-N-[(3-chlorophenyl)sulfonyl]-3-oxo-2-quinoxalinecarboxamide; 64% yield; m.p. 320°C.

Calcd: C, 41.64; H, 1.86; N, 9.71; Cl, 24.58; S, 7.41.

Found: C, 41.58; H, 1.87; N, 9.60; Cl, 24.90; S, 6.99.

EXAMPLE 39

6,7-Dichloro-3,4-dihydro-N-[(2-chlorophenyl)sulfonyl]-3-oxo-2-quinoxalinecarboxamide; 22% yield;
m.p. 317-318°C.

Calcd: C, 41.64; H, 1.86; N, 9.71; Cl, 24.58; S, 7.41.

Found: C, 41.63; H, 1.17; N, 9.82; Cl, 24.29; S, 7.91.

EXAMPLE 40

6,7-Dichloro-3,4-dihydro-N-(2-naphthalenylsulfonyl)-3-oxo-2-quinoxalinecarboxamide; 32% yield;
m.p. 306-308°C.

Calcd: C, 50.91; H, 2.47; N, 9.37; Cl, 15.82; S, 7.15.

Found: C, 51.03; H, 2.11; N, 9.39; Cl, 15.86; S, 7.10.

EXAMPLE 41

6,7-Dichloro-3,4-dihydro-3-oxo-N-[(3-nitrophenyl)-sulfonyl]-2-quinoxalinecarboxamide; 55% yield;
m.p. 325-327°C.

Calcd: C, 40.65; H, 1.82; N, 12.64; Cl, 16.00; S, 7.23.

Found: C, 40.42; H, 1.46; N, 12.55; Cl, 16.04; S, 7.56.

EXAMPLE 42

6,7-Dichloro-3,4-dihydro-3-oxo-N-[(4-nitrophenyl)-sulfonyl]-2-quinoxalinecarboxamide; 55% yield;
m.p. 316-319°C.

Calcd: C, 40.65; H, 1.82; N, 12.64; Cl, 16.00; S, 7.23.

Found: C, 40.55; H, 1.66; N, 12.58; Cl, 16.40; S, 7.10.

EXAMPLE 43

6,7-Dichloro-3,4-dihydro-3-oxo-N-[(2-nitrophenyl)-sulfonyl]-2-quinoxalinecarboxamide; 77% yield; m.p. 313-317°C.

Calcd: C, 40.65; H, 1.82; N, 12.64; Cl, 16.00; S, 7.23.

Found: C, 40.74; H, 1.85; N, 12.40; Cl, 16.64; S, 6.81.

EXAMPLE 44

6,7-Dichloro-3,4-dihydro-3-oxo-N-[[2,4,6-tris(1-methylethyl)phenyl]sulfonyl]-2-quinoxalinecarboxamide; 12% yield; m.p. 289°C.

Calcd: C, 54.96; H, 5.19; N, 8.01; Cl, 13.52; S, 6.11.

Found: C, 54.71; H, 5.04; N, 8.00; Cl, 13.21; S, 5.99.

EXAMPLE 45

6,7-Dichloro-3,4-dihydro-3-oxo-N-[(2-fluorophenyl)-sulfonyl]-2-quinoxalinecarboxamide; 30% yield; m.p. 312-314°C.

Calcd: C, 43.29; H, 1.94; N, 10.10; Cl, 17.04; F, 4.56; S, 7.70.

Found: C, 43.09; H, 1.63; N, 10.04; Cl, 17.38; F, 4.90; S, 7.53.

EXAMPLE 46

6,7-Dichloro-3,4-dihydro-3-oxo-N-[(pentamethylphenyl)-sulfonyl]-2-quinoxalinecarboxamide; 36% yield; m.p. 270°C.

Calcd: C, 51.29; H, 4.09; N, 8.97; S, 6.85.

Found: C, 51.11; H, 3.81; N, 8.94; S, 6.95.

EXAMPLE 47

N-[(1,2-Benzisoxazol-3-ylmethyl)sulfonyl]-6,7-dichloro-3,4-dihydro-3-oxo-2-quinoxalinecarboxamide; 56% yield; m.p. 283-285°C.

Calcd: C, 45.05; H, 2.22; N, 12.36; Cl, 15.64; S, 7.07.

Found: C, 44.77; H, 2.25; N, 12.27; Cl, 16.04; S, 6.92.

The following additional preparations of compounds here are within procedures as set out in U.S. Patent No. 4,264,600.

PREPARATION 4

Ethyl-6,7-dimethyl-3,4-dihydro-3-oxo-2-quinoxaline-carboxylate

PREPARATION 5

6,7-Dimethyl-3,4-dihydro-3-oxo-2-quinoxaline-carboxylate; 97% yield; m.p. 304-308°C.

Analysis for 2 mole H_2O:

Calcd: C, 59.22; H, 4.76; N, 12.56.

Found: C, 59.22; H, 4.41; N, 12.62.

PREPARATION 6

Ethyl-3,4-dihydro-3-oxo-benzo(g)-quinoxaline-2-carboxylate; 79% yield; m.p. 205°C.

Calcd: C, 67.16; H, 4.51; N, 10.44.

Found: C, 67.35; H, 4.51; N, 10.68.

PREPARATION 7

Ethyl-5,8-dibromo-3,4-dihydro-3-oxo-quinoxaline-2-carboxylate; 89% yield; m.p. 205°C.

Calcd: C, 35.14; H, 2.14; N, 7.45.

Found: C, 35.05; H, 1.94; N, 6.99.

PREPARATION 8

5,8-Dibromo-3,4-dihydro-3-oxo-quinoxaline-2-carboxylic acid; 74% yield; m.p. 280-283°C.

Calcd: C, 31.07; H, 1.16; N, 8.05; Br, 45.93.

Found: C, 30.97; H, 1.15; N, 8.10; Br, 48.30.

PREPARATION 9

Ethyl-6,7-dibromo-3,4-dihydro-3-oxo-quinoxaline-2-carboxylate; 78% yield; m.p. 238°C.

Calcd: C, 35.14; H, 2.14; N, 7.45; Br, 42.50.

Found: C, 35.22; H, 2.09; N, 6.92; Br, 42.76.

PREPARATION 10

6,7-Dibromo-3,4-dihydro-3-oxo-quinoxaline-2-carboxylic acid; 82% yield; m.p. >300°C.

Calcd: C, 31.07; H, 1.16; N, 8.05.

Found: C, 31.18; H, 1.32; N, 8.32.

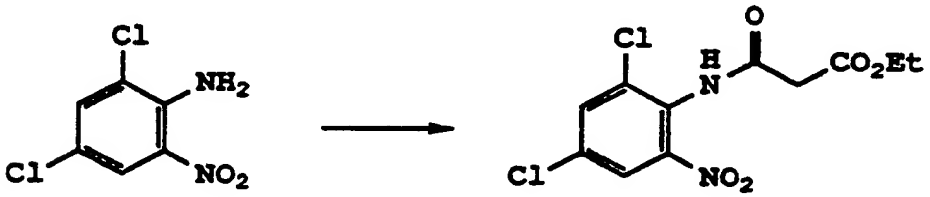
PREPARATION 11

Ethyl-6,7-dinitro-3,4-dihydro-3-oxo-quinoxaline-2-carboxylate; 36% yield; m.p. 220°C.

Calcd: C, 42.87; H, 2.62; N, 18.18.

Found: C, 42.54; H, 2.52; N, 17.78.

PREPARATION 1a

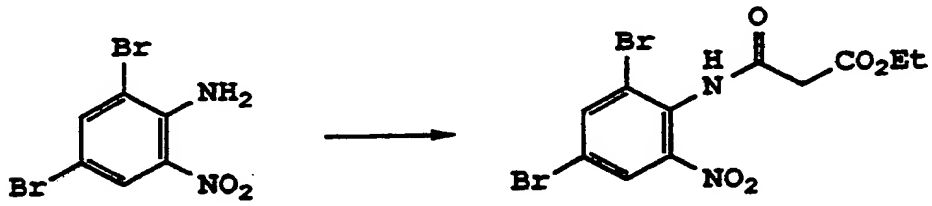


Ethyl 3-[(2,4-dichloro-6-nitrophenyl)amino]-3-oxopropanoate

A solution of 4,6-dichloro-2-nitroaniline (31.0 g, 0.15 mol) and chloroethylmalonate (25.0 g,

0.17 mol) in toluene (500 mL) was heated at reflux for 24 hours. The reaction mixture was cooled and concentrated. The residue was dissolved in hot ethanol, decolorized with charcoal, and filtered. The solid which formed on cooling was collected by suction filtration and dried to give the title compound as a yellow solid (13.6 g, 28%).

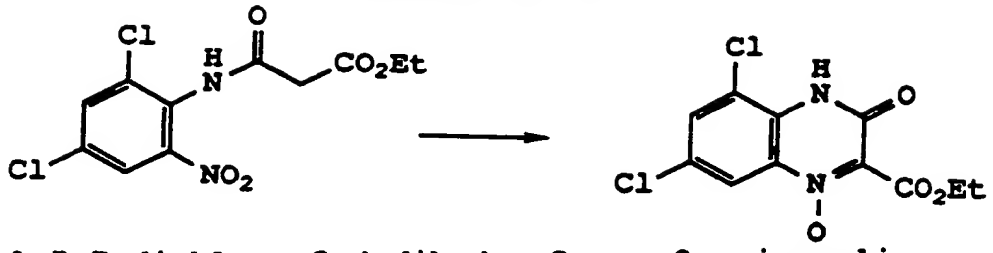
PREPARATION 2a



Ethyl 3-[(2,4-dibromo-6-nitrophenyl)amino]-3-oxopropanoate

A solution of 4,6-dibromo-2-nitroaniline (44.3 g, 0.15 mol) and chloroethylmalonate (25.0 g, 0.17 mol) in toluene (500 mL) was heated at reflux for 24 hours. The reaction mixture was cooled and the solid which formed was collected by suction filtration. The solid was suspended in diisopropyl ether, filtered, and dried under vacuum to give the title compound as a

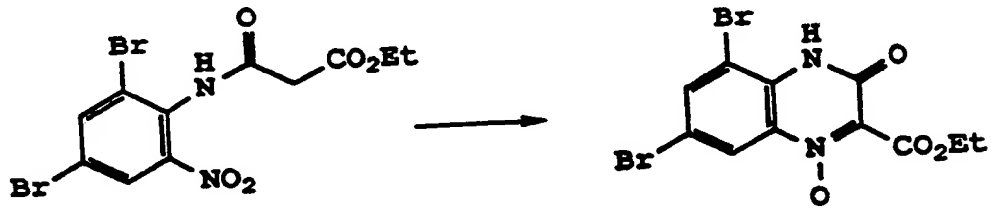
PREPARATION 3a



Ethyl 5,7-dichloro-3,4-dihydro-3-oxo-2-quinoxaline-carboxylate 1-oxide

Sodium (2.57 g, 0.112 mol) was dissolved in ethanol (500 mL) and the resulting solution was treated with the product from Preparation 1a (22.7 g, 71.0 mmol) in one portion and the resulting solution was heated to reflux for 45 minutes. The reaction mixture cooled to 0°C and treated with 1N HCl (125 mL). The solid which formed was collected by suction filtration and crystallized from hot ethanol to give the title compound as a yellow solid (9.84 g, 46%).

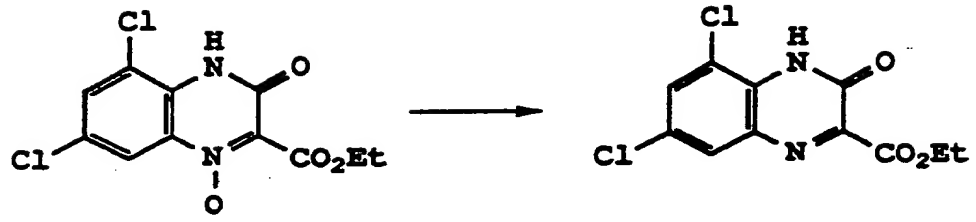
PREPARATION 4a



Ethyl 5,7-dibromo-3,4-dihydro-3-oxo-2-quinoxaline-carboxylate 1-oxide

In a manner similar to that described in Preparation 3a, the product of Preparation 2a (30.0 g) was converted to the title compound as a yellow solid (13.3 g, 46%).

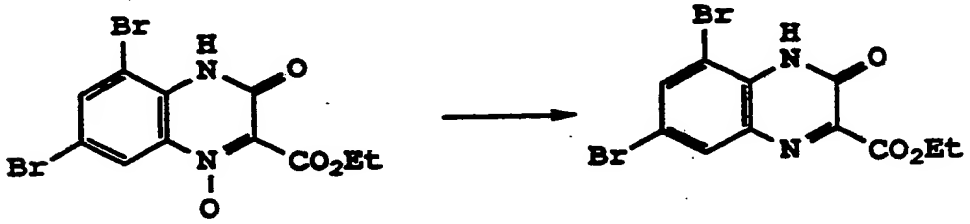
PREPARATION 5a



Ethyl 5,7-dichloro-3,4-dihydro-3-oxo-2-quinoxaline-carboxylate

A solution of the product from Preparation 3a (5.00 g, 17.3 mmol) and phosphorous trichloride (30 mL) in tetrahydrofuran (200 mL) was heated at reflux for 24 hours. The reaction was cooled and poured over ice. The resulting suspension was extracted into CH_2Cl_2. The organic phase was washed with water, dried (Na_2SO_4), and concentrated. The residue was suspended in EtOH, collected by suction filtration, and dried to give the title compound as a yellow solid (1.67 g, 34%).

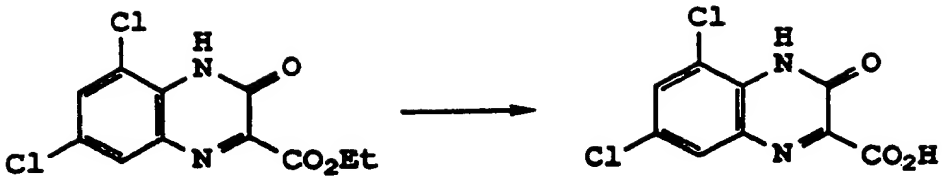
PREPARATION 6a



Ethyl 5,7-dibromo-3,4-dihydro-3-oxo-2-quinoxaline-carboxylate

In a manner similar to that described in Preparation 5a, the product of Preparation 4a (13.4 g, 34.2 mmol) was converted to the title compound as a yellow solid (3.64 g, 28%).

PREPARATION 7a

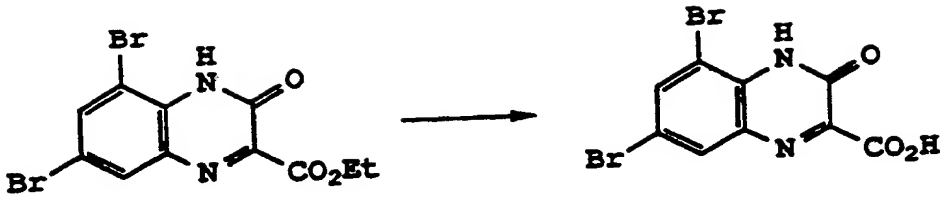


5,7-Dichloro-3,4-dihydro-3-oxo-2-quinoxalinecarboxylic acid

A solution of the product from Preparation 5a (2.14 g, 8.26 mmol) and potassium hydroxide (2.08 g, 37.1 mmol) in 3:1 water/iPrOH (100 mL) was heated at reflux for 2 hours. The reaction mixture was cooled to room temperature and acidified to pH 1 with concentrated HCl. The solid which formed was collected by suction filtration and dried to give the title compound as a yellow solid (1.86 g, 87%), m.p. 196-198°C.

Elemental analysis calculated for $C_9H_4Cl_2N_2O_3$:
C, 41.73; H, 1.56; N, 10.81.
Found: C, 41.43; H, 1.33; N, 10.77.

PREPARATION 8a



5,7-Dibromo-3,4-dihydro-3-oxo-2-quinoxalinecarboxylic acid

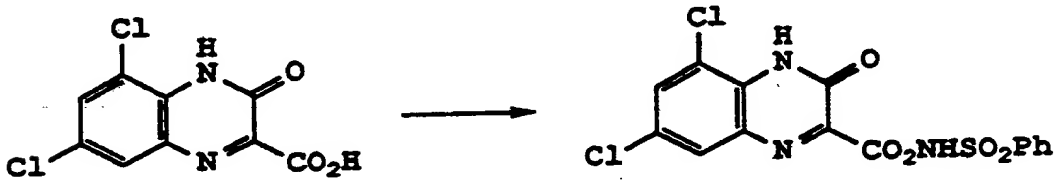
In a manner similar to that described in Preparation 7a, the product of Preparation 6a (2.41 g, 6.41 mmol) was converted to the title compound as a yellow solid (2.41 g, 34%), m.p. 202-206°C.

Elemental analysis calculated for $C_9H_4Br_2N_2O_3$:

C, 31.07; H, 1.06; N, 8.05.

Found: C, 31.26; H, 1.01; N, 8.20

PREPARATION 9a



5,7-Dichloro-3,4-dihydro-3-oxo-N-(phenylsulfonyl)-2-quinoxalinecarboxamide

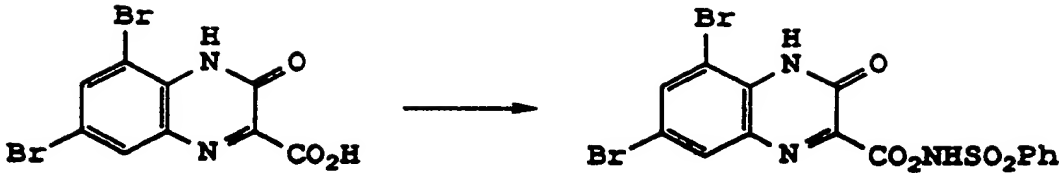
In a manner similar to that described in Preparation 10a, the product of Preparation 7a (0.50 g, 1.93 mmol) was converted to the title compound as a yellow solid (0.55 g, 71%), m.p. 286-290°C.

Elemental analysis calculated for $C_{15}H_9Cl_2N_3O_4S$:

C, 45.24; H, 2.28; N, 10.55; S, 8.05.

Found: C, 44.90; H, 2.16; N, 10.31; S, 7.74.

PREPARATION 10a



5,7-Dibromo-3,4-dihydro-3-oxo-N-(phenylsulfonyl)-2-quinoxalinecarboxamide

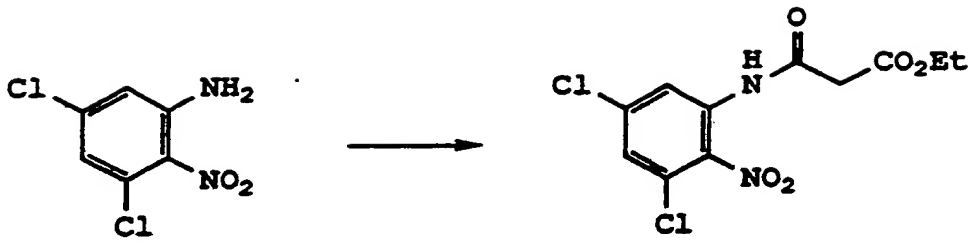
A solution of the product from Preparation 8a (0.50 g, 1.44 mmol) in DMF (12 mL) was treated with carbonyl diimidazole (0.70 g) and the resulting solution was heated at 60°C for 4 hours. Concurrently a suspension of benzenesulfonamide (0.67 g, 4.26 mmol) and NaH (0.17 g, 4.57 mmol) in DMF (10 mL) was stirred for 4 hours at room temperature. The two reaction mixtures were combined and the resulting solution was stirred at room temperature overnight. The reaction mixture was poured onto ice and 1N HCl. The solid which formed was collected by suction filtration, washed with water, and dried under vacuum (P_2O_5) to give the title compound as a yellow solid (0.44 g, 63%), m.p. 290-293°C.

Elemental analysis calculated for $C_{15}H_{19}Br_2N_3O_4S$:

C, 36.98; H, 1.86; N, 8.63; S, 6.58.

Found: C, 36.80; H, 1.71; N, 8.43; S, 6.57.

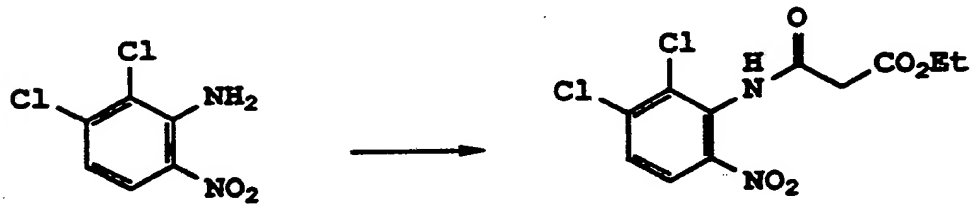
PREPARATION 11a



Ethyl 3-[(3,5-dichloro-2-nitrophenyl)amino]-3-oxopropanoate

In a manner similar to that described in Preparation 1a, 3,5-dichloro-2-nitroaniline (47.5 g, 0.229 mol) was converted to the title compound as a yellow solid (51.7 g, 70%).

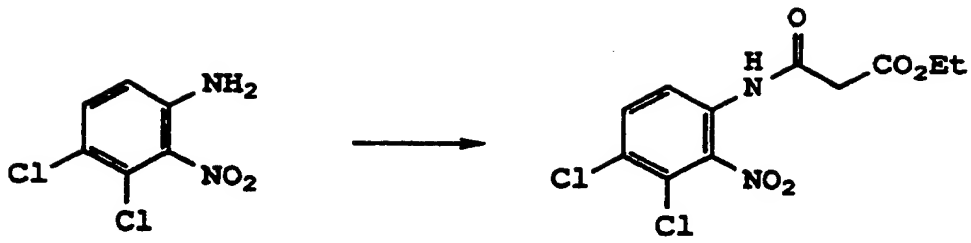
PREPARATION 12a



Ethyl 3-[(2,3-dichloro-6-nitrophenyl)amino]-3-oxopropanoate

In a manner similar to that described in Preparation 1a, 5,6-dichloro-2-nitroaniline is converted to the title compound.

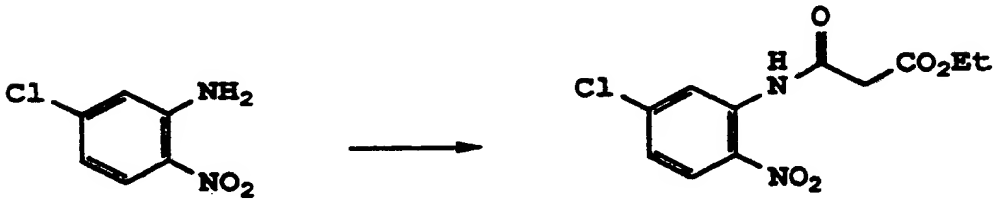
PREPARATION 13a



Ethyl 3-[(3,4-dichloro-2-nitrophenyl)amino]-3-oxopropanoate

In a manner similar to that described in Preparation 1a, 3,4-dichloro-2-nitroaniline is converted to the title compound.

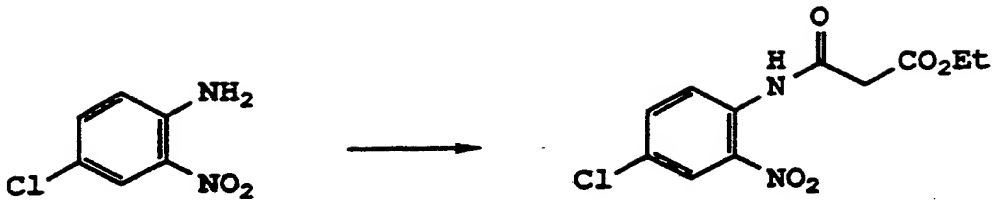
PREPARATION 14a



Ethyl 3-[(5-chloro-2-nitrophenyl)amino]-3-oxopropanoate

In a manner similar to that described in Preparation 1a, 5-chloro-2-nitroaniline (26.0 g, 0.15 mol) is converted to the title compound as a yellow solid (34.5 g, 80%).

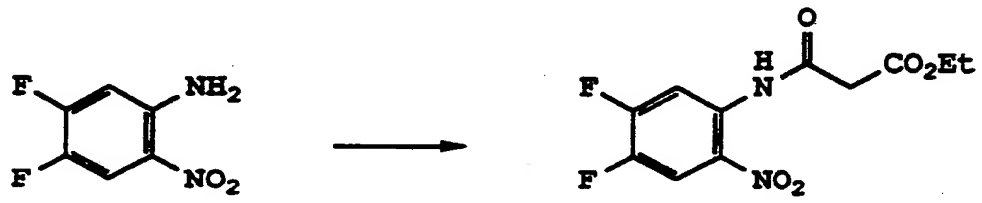
PREPARATION 15a



Ethyl 3-[(4-chloro-2-nitrophenyl)amino]-3-oxopropanoate

In a manner similar to that described in Preparation 1a, 4-chloro-2-nitroaniline (26.0 g, 0.15 mol) is converted to the title compound as a yellow solid (33.8 g, 78%).

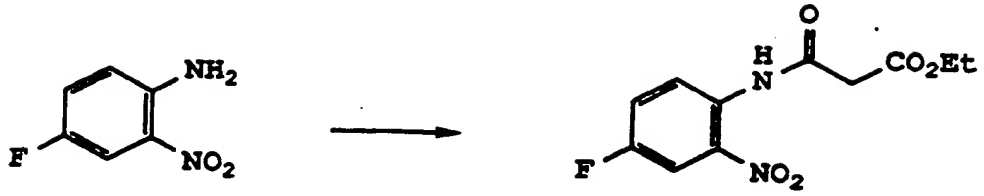
PREPARATION 16a



Ethyl 3-[(4,5-difluoro-2-nitrophenyl)amino]-3-oxopropanoate

In a manner similar to that described in Preparation 1a, 4,5-difluoro-2-nitroaniline (20.0 g, 0.115 mol) is converted to the title compound as a yellow solid.

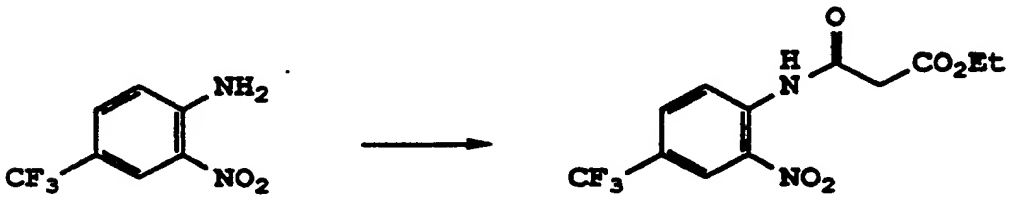
PREPARATION 17a



Ethyl 3-[(4-fluoro-2-nitrophenyl)amino]-3-oxopropanoate

In a manner similar to that described in Preparation 1a, 4-fluoro-2-nitroaniline (21.6 g, 0.138 mol) is converted to the title compound as a yellow solid (19.4 g, 52%).

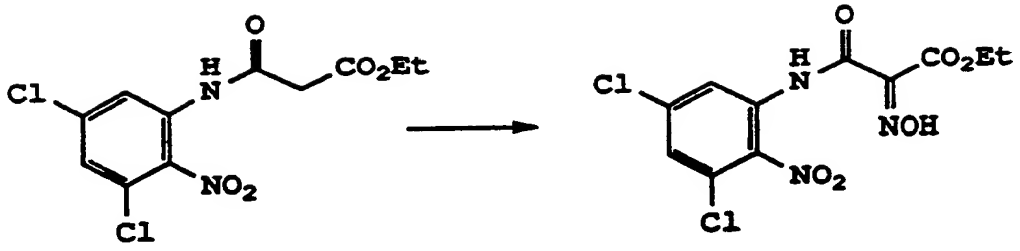
PREPARATION 18a



Ethyl 3-[[2-nitro-4-(trifluoromethyl)phenyl]amino]-3-oxopropanoate

In a manner similar to that described in Preparation 1a, 4-amino-3-nitrobenzotrifluoride (31.1 g, 0.151 mol) is converted to the title compound as a yellow solid (31.9 g, 66%).

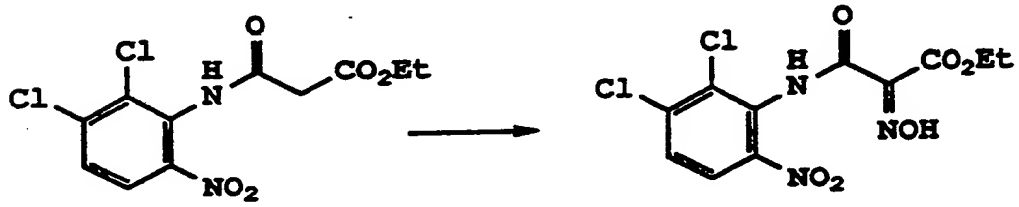
PREPARATION 19a



Ethyl 3-[(3,5-dichloro-2-nitrophenyl)amino]-2-(hydroxyimino)-3-oxopropanoate

A solution of the product from Preparation 11a (7.00 g, 23.9 mmol) in 4:2:1 AcOH/THF/H_2O (210 mL) was treated with $NaNO_2$ (1.81 g, 26.3 mmol) in one portion and stirred at room temperature for 4 hours. Additional $NaNO_2$ (1.81 g, 26.3 mmol) was added and stirring was continued overnight. The reaction was extracted into CH_2Cl_2, dried ($MgSO_4$), filtered, and concentrated to give the title compound as a yellow solid (4.33 g, 76%).

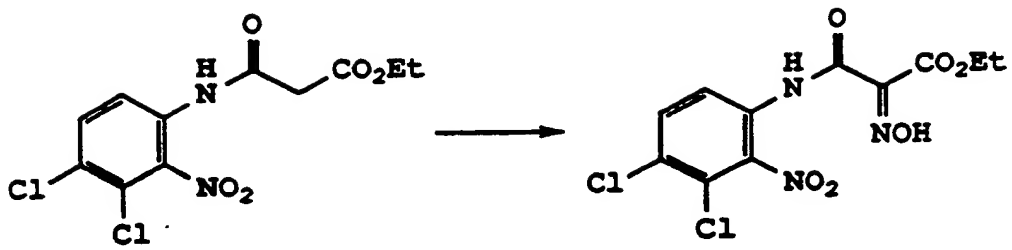
PREPARATION 20a



Ethyl 3-[(2,3-dichloro-2-nitrophenyl)amino]-2-(hydroxyimino)-3-oxopropanoate

In a manner similar to that described in Preparation 19a, the product from Example 12a is converted to the title compound.

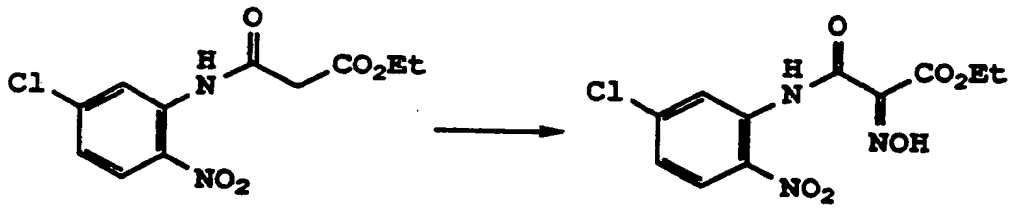
PREPARATION 21a



Ethyl 3-[(3,4-dichloro-2-nitrophenyl)amino]-2-(hydroxyimino)-3-oxopropanoate

In a manner similar to that described in Preparation 19a, the product from Preparation 13a is converted to the title compound.

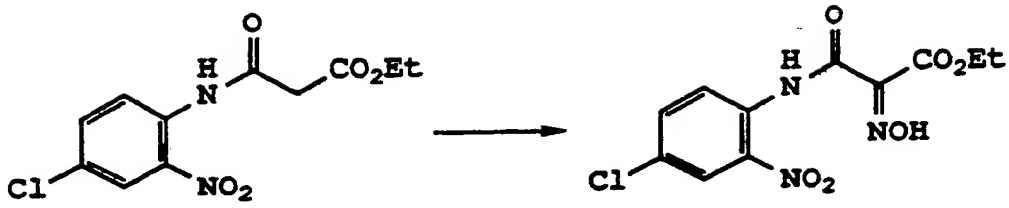
PREPARATION 22a



Ethyl 3-[(5-chloro-2-nitrophenyl)amino]-2-(hydroxyimino)-3-oxopropanoate

In a manner similar to that described in Preparation 19a, the product from Preparation 14a (10.0 g, 36.7 mmol) is converted to the title compound as a yellow solid (9.24 g, 80%).

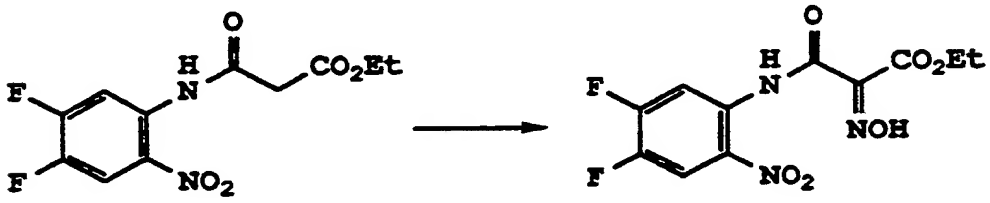
PREPARATION 23a



Ethyl 3-[(4-chloro-2-nitrophenyl)amino]-2-(hydroxyimino)-3-oxopropanoate

In a manner similar to that described in Preparation 19a, the product from Preparation 15a (10.0 g, 36.7 mmol) is converted to the title compound as a yellow solid (9.83 g, 85%).

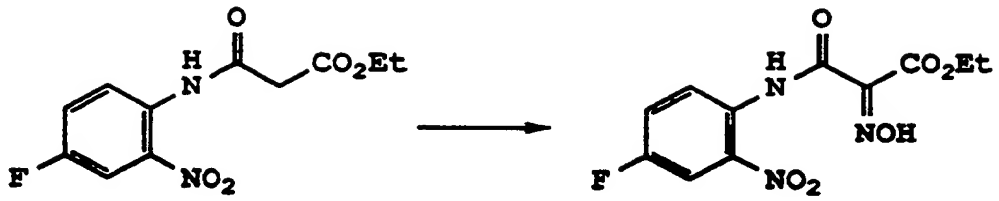
PREPARATION 24a



Ethyl 3-[(4,5-difluoro-2-nitrophenyl)amino]-2-(hydroxyimino)-3-oxopropanoate

In a manner similar to that described in Preparation 19a, the product from Preparation 16a is converted to the title compound.

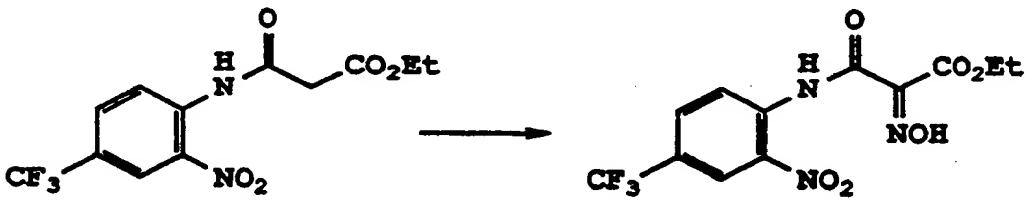
PREPARATION 25a



Ethyl 3-[(4-fluoro-2-nitrophenyl)amino]-2-(hydroxyimino)-3-oxopropanoate

In a manner similar to that described in Preparation 19a, the product from Preparation 17a is converted to the title compound.

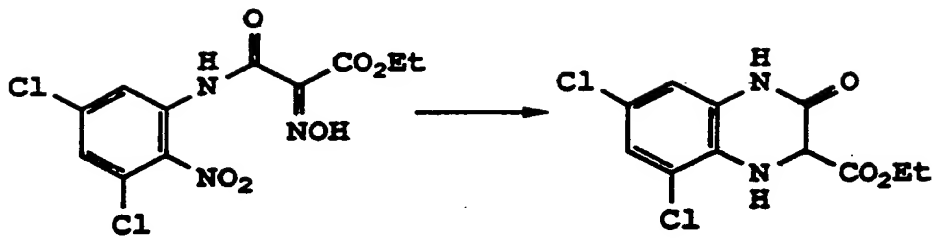
PREPARATION 26a



Ethyl 2-(hydroxyimino)-3-[[2-nitro-4-(trifluoromethyl)phenyl]amino]-3-oxopropanoate

In a manner similar to that described in Preparation 19a, the product from Preparation 18a (10.0 g, 31.2 mmol) is converted to the title compound as a yellow solid (9.49 g, 87%).

PREPARATION 27a

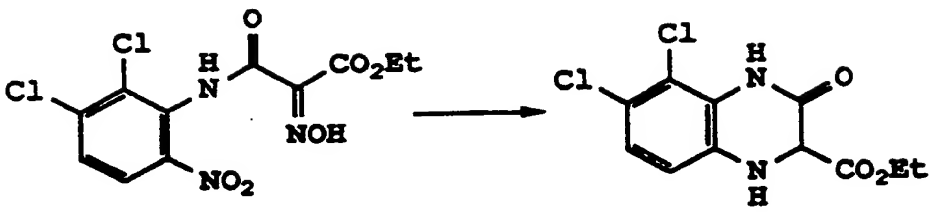


Ethyl 6,8-dichloro-1,2,3,4-tetrahydro-3-oxo-2-quinoxalinecarboxylate

A solution of the product from Preparation 19a (8.00 g, 22.8 mmol) in THF (200 mL) was hydrogenated over RaNi (1.00 g) for 3 hours. The reaction mixture was filtered and concentrated and the residue was dissolved in dioxane (300 mL) and treated with $TiCl_3$ (53 mL of a 1.3 M solution in H_2O). The resulting purple-colored solution was stirred at room temperature until the color was discharged. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution. The resulting suspension was extracted with 1:1 EtOAc/THF and concentrated. The residue was suspended in EtOH and collected to give the title compound as a tan solid (3.50 g, 53%); m.p. 244-250°C.

Elemental analysis calculated for $C_{11}H_{11}Cl_2N_2O_3$:
C, 45.70; H, 3.49; N, 9.69.
Found: C, 45.67; H, 3.20; N, 9.53.

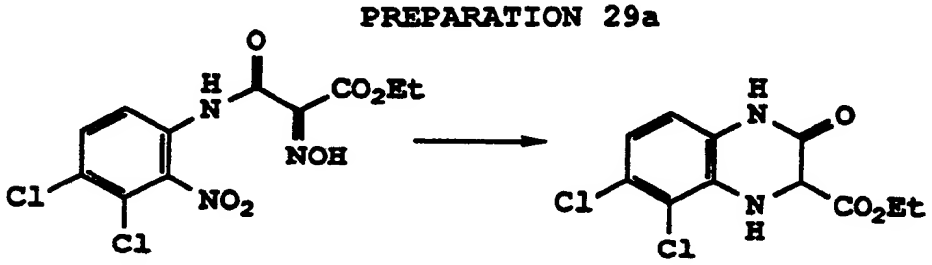
PREPARATION 28a



Ethyl 5,6-dichloro-1,2,3,4-tetrahydro-3-oxo-2-quinoxalinecarboxylate

In a manner similar to that described in Preparation 27a, the product from Preparation 20a is converted to the title compound.

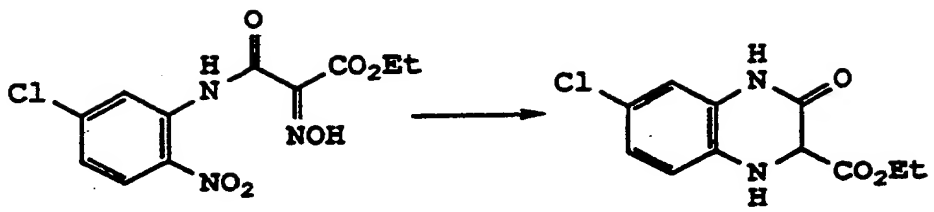
PREPARATION 29a



Ethyl 7,8-dichloro-1,2,3,4-tetrahydro-3-oxo-2-quinoxalinecarboxylate

In a manner similar to that described in

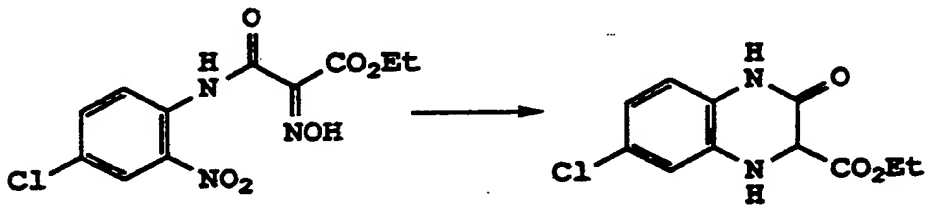
PREPARATION 30a



Ethyl 6-chloro-1,2,3,4-tetrahydro-3-oxo-2-quinoxaline-carboxylate

In a manner similar to that described in Preparation 27a, the product from Preparation 22a is converted to the title compound.

PREPARATION 31a



Ethyl 7-chloro-1,2,3,4-tetrahydro-3-oxo-2-quinoxaline-carboxylate

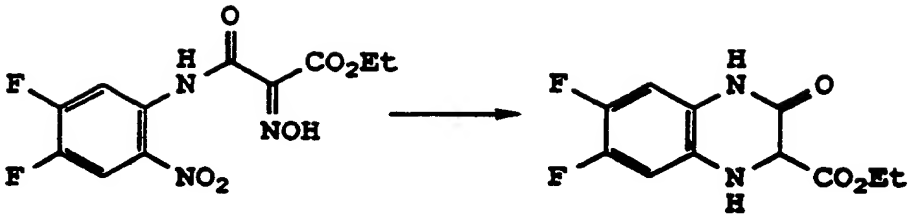
In a manner similar to that described in Preparation 27a, the product from Preparation 23a (8.00 g, 25.3 mmol) is converted to the title compound as a yellow solid (2.11 g, 33%); m.p. 196-198°C.

Elemental analysis calculated for $C_{11}H_{11}ClN_2O_3$:

C, 51.88; H, 4.35; N, 11.00; Cl, 13.92

Found: C, 52.05; H, 3.76; N, 10.81; Cl, 14.24.

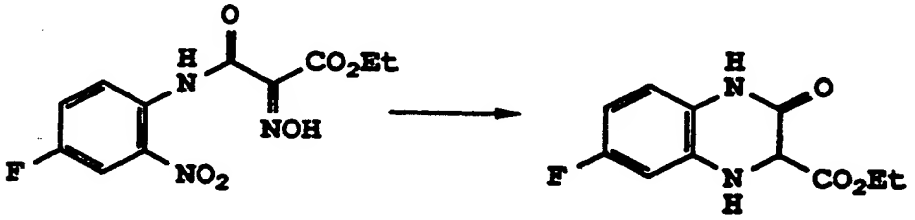
PREPARATION 32a



Ethyl 6,7-difluoro-1,2,3,4-tetrahydro-3-oxo-2-quinoxalinecarboxylate

In a manner similar to that described in Preparation 27a, the product from Preparation 24a is converted to the title compound.

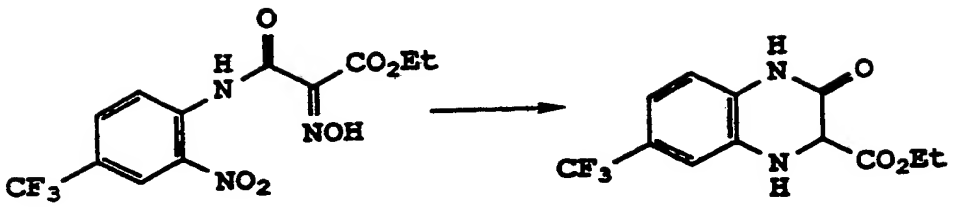
PREPARATION 33a



Ethyl 7-fluoro-1,2,3,4-tetrahydro-3-oxo-2-quinoxaline-carboxylate

In a manner similar to that described in Preparation 27a, the product from Preparation 25a is converted to the title compound.

PREPARATION 34a



Ethyl 1,2,3,4-tetrahydro-3-oxo-7-(trifluoromethyl)-2-quinoxalinecarboxylate

In a manner similar to that described in Preparation 27a, the product from Preparation 26a (8.00 g, 22.9 mmol) is converted to the title compound as a yellow solid (3.39 g, 52%); m.p. 178-180°C.

Elemental analysis calculated for $C_{12}H_{11}F_3N_2O_3$:

C, 50.01; H, 3.85; N, 9.72.

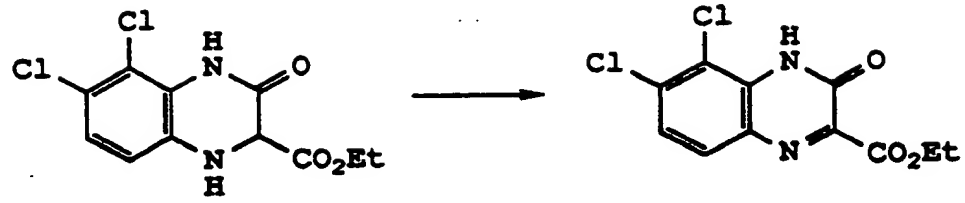
Found: C, 50.29; H, 3.52; N, 9.35.

PREPARATION 35a

Ethyl 6,8-dichloro-3,4-dihydro-3-oxo-2-quinoxaline-carboxylate

A solution of the product from Preparation 27a (1.00 g, 3.46 mmol) in THF (150 mL) was treated with bromine (3.5 mL of a 1M solution in CH_2Cl_2). The reaction mixture was stirred for 30 minutes and concentrated to give the title compound as a yellow solid (0.98 g, 98%).

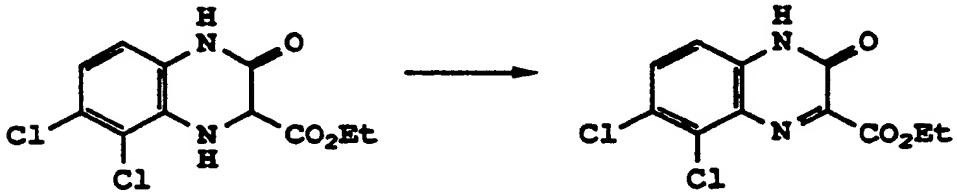
PREPARATION 36a



Ethyl 5,6-dichloro-3,4-dihydro-3-oxo-2-quinoxaline-carboxylate

In a manner similar to that described in Preparation 39a, the product from Preparation 28a is converted to the title compound.

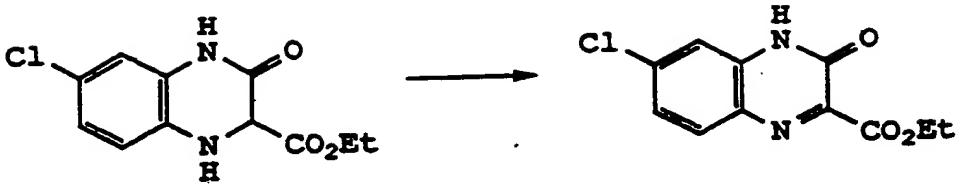
PREPARATION 37a



Ethyl 7,8-dichloro-3,4-dihydro-3-oxo-2-quinoxaline-carboxylate

In a manner similar to that described in Preparation 39a, the product from Preparation 29a is converted to the title compound.

PREPARATION 38a



Ethyl 6-chloro-3,4-dihydro-3-oxo-2-quinoxaline-carboxylate

In a manner similar to that described in Preparation 39a, the product from Preparation 30a is converted to the title compound.

PREPARATION 39a

Ethyl 7-chloro-3,4-dihydro-3-oxo-2-quinoxaline-carboxylate

A solution of the product from Preparation 31a (0.50 g, 1.96 mmol) in dioxane (15 mL) was treated with DDQ (0.47 g, 2.06 mmol). The reaction was stirred at room temperature for 15 minutes and filtered. The filtrate was concentrated and crystallized from hot EtOH. The solid which formed on cooling was collected by suction filtration to give the title compound as a yellow solid (0.43 g, 87%).

PREPARATION 40a

Ethyl 6,7-difluoro-3,4-dihydro-3-oxo-2-quinoxaline-carboxylate

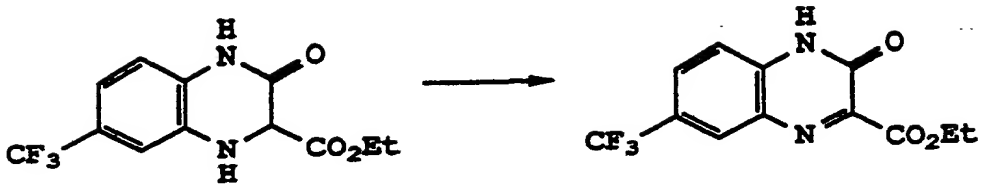
In a manner similar to that described in Preparation 39a, the product from Preparation 32a is converted to the title compound.

PREPARATION 41a

Ethyl 7-fluoro-3,4-dihydro-3-oxo-2-quinoxaline-carboxylate

In a manner similar to that described in Preparation 39a, the product from Preparation 33a is converted to the title compound.

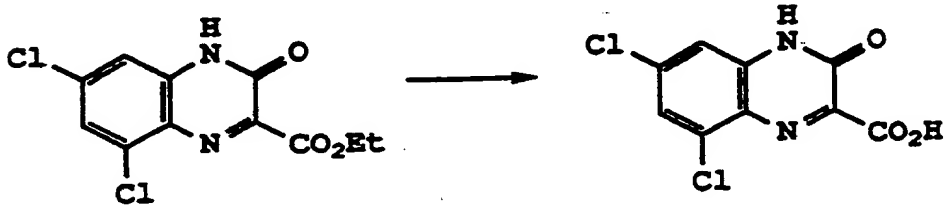
PREPARATION 42a



Ethyl 3,4-dihydro-3-oxo-7-(trifluoromethyl)-2-quinoxalinecarboxylate

In a manner similar to that described in Preparation 39a, the product from Preparation 34a (0.50 g, 1.73 mmol) is converted to the title compound as a tan solid (0.32 g, 65%).

PREPARATION 43a



6,8-Dichloro-3,4-dihydro-3-oxo-2-quinoxalinecarboxylic acid

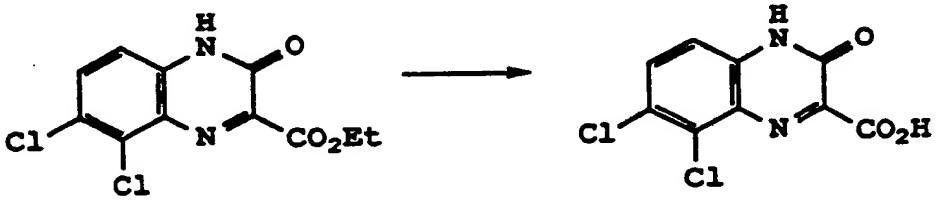
In a manner similar to that described in Preparation 7a, the product from Preparation 35a is converted to the title compound.

PREPARATION 44a

5,6-Dichloro-3,4-dihydro-3-oxo-2-quinoxalinecarboxylic acid

In a manner similar to that described in Preparation 7a, the product from Preparation 36a is converted to the title compound.

PREPARATION 45a



7,8-Dichloro-3,4-dihydro-3-oxo-2-quinoxalinecarboxylic acid

In a manner similar to that described in Preparation 7a, the product from Preparation 37a is converted to the title compound.

PREPARATION 46a

6-Chloro-3,4-dihydro-3-oxo-2-quinoxalinecarboxylic acid

In a manner similar to that described in Preparation 7a, the product from Preparation 38a is converted to the title compound.

PREPARATION 47a

7-Chloro-3,4-dihydro-3-oxo-2-quinoxalinecarboxylic acid

In a manner similar to that described in Preparation 7a, the product from Preparation 39a is converted to the title compound.

PREPARATION 48a

6,7-Difluoro-3,4-dihydro-3-oxo-2-quinoxalinecarboxylic acid

In a manner similar to that described in Preparation 7a, the product from Preparation 40a is converted to the title compound.

PREPARATION 49a

7-Fluoro-3,4-dihydro-3-oxo-2-quinoxalinecarboxylic acid

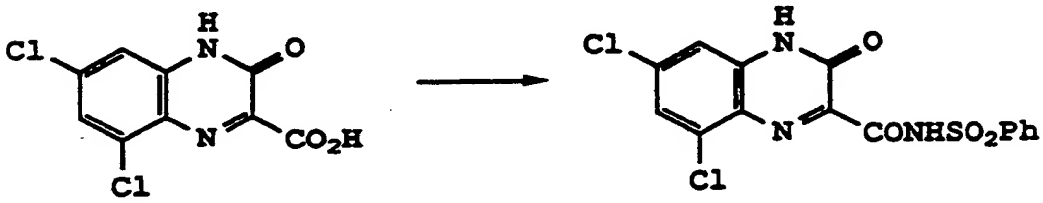
In a manner similar to that described in Preparation 7a, the product from Preparation 41a is converted to the title compound.

PREPARATION 50a

3,4-Dihydro-3-oxo-7-(trifluoromethyl)-2-quinoxaline-carboxylic acid

In a manner similar to that described in Preparation 7a, the product from Preparation 42a is converted to the title compound.

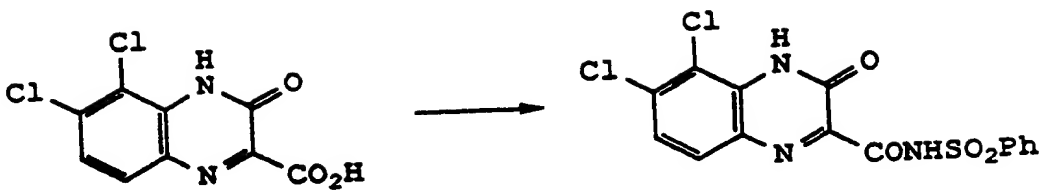
EXAMPLE 48



6,8-Dichloro-3,4-dihydro-3-oxo-N-(phenylsulfonyl)-2-quinoxalinecarboxamide

In a manner similar to that described in Preparation 10a, the product from Preparation 43a is converted to the above compound.

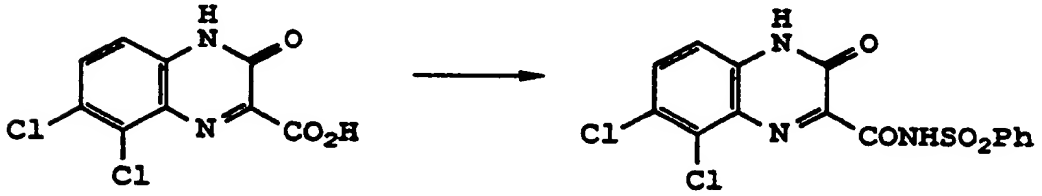
EXAMPLE 49



5,6-Dichloro-3,4-dihydro-3-oxo-N-(phenylsulfonyl)-2-quinoxalinecarboxamide

In a manner similar to that described in Preparation 10a, the product from Preparation 44a is converted to the above compound.

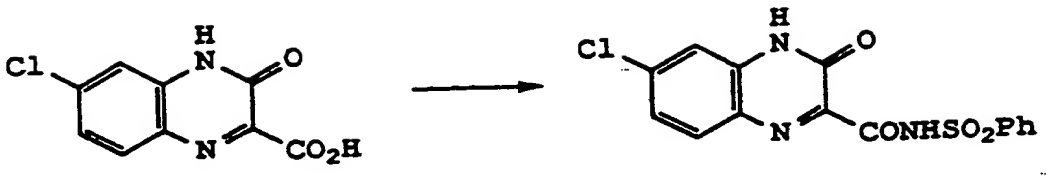
EXAMPLE 50



7,8-Dichloro-3,4-dihydro-3-oxo-N-(phenylsulfonyl)-2-quinoxalinecarboxamide

In a manner similar to that described in Preparation 10a, the product from Preparation 45a is converted to the above compound.

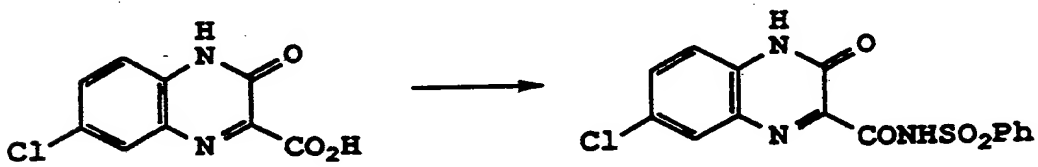
EXAMPLE 51



6-Chloro-3,4-dihydro-3-oxo-N-(phenylsulfonyl)-2-quinoxalinecarboxamide

In a manner similar to that described in Preparation 10a, the product from Preparation 46a is converted to the above compound.

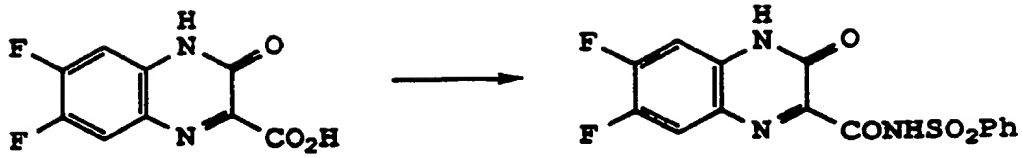
EXAMPLE 52



7-Chloro-3,4-dihydro-3-oxo-N-(phenylsulfonyl)-2-quinoxalinecarboxamide

In a manner similar to that described in Preparation 10a, the product from Preparation 47a is converted to the above compound.

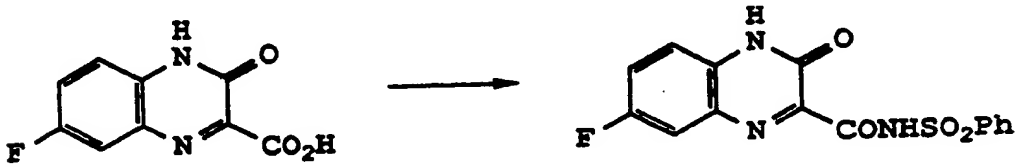
EXAMPLE 53



6,7-Difluoro-3,4-dihydro-3-oxo-N-(phenylsulfonyl)-2-quinoxalinecarboxamide

In a manner similar to that described in Preparation 10a, the product from Preparation 48a is converted to the above compound.

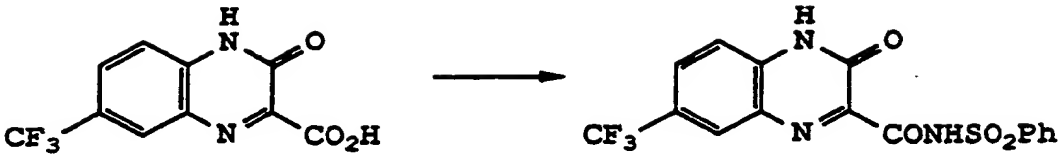
EXAMPLE 54



7-Fluoro-3,4-dihydro-3-oxo-N-(phenylsulfonyl)-2-quinoxalinecarboxamide

In a manner similar to that described in Preparation 10a, the product from Preparation 49a is converted to the above compound.

EXAMPLE 55



3,4-Dihydro-3-oxo-N-(phenylsulfonyl)-7-(trifluoromethyl)-2-quinoxalinecarboxamide

In a manner similar to that described in Preparation 10a, the product from Preparation 50a is converted to the above compound.

BIOLOGICAL TESTING

Specifically, the compounds of the present invention have activity as antagonists at the strychnine insensitive glycine receptor which is located on the NMDA receptor complex. As such, the compounds of the present invention are NMDA receptor antagonists. Also, the compounds of the present invention have activity as AMPA and kainate receptor antagonists.

For example, compounds of the invention exhibit valuable biological properties because of these excitatory amino acid antagonizing properties.

The glycine binding assay is performed as described by W. Frost White, et al, Journal of Neurochemistry 1989;53(2):503-12.

Selected compounds having the Formula I of the present invention are tested in the glycine binding assay and provide the following data expressed as % inhibition at the dose expressed as molar concentration.

TABLE I
(Page 1 of 2)

Example No.	Molar Conc.	% Inhibition
1	1.00E-4	89
2	5.00E-5	23
3	1.00E-4	38
4	1.00E-4	71
6	1.00E-4	55
9	1.00E-4	73
10	1.00E-4	40
11	1.00E-4	85
12	5.00E-6	53
13	1.00E-4	55
14	1.00E-4	64
16	1.00E-4	91
17	1.00E-4	92
18	1.00E-4	18
19	1.00E-4	94
21	5.00E-5	29
22	5.00E-5	25
23	1.00E-4	36
24	1.00E-4	68
25	5.00E-5	90
26	5.00E-5	75
27	1.00E-4	42
28	1.00E-4	72
29	1.00E-4	88
31	1.00E-4	100

TABLE I
(Page 2 of 2)

Example No.	Molar Conc.	% Inhibition
32	1.00E-4	76
33	1.00E-5	76
34	1.00E-4	81
35	1.00E-4	83
36	5.00E-4	100
37	5.00E-5	100
38	1.00E-4	83
40	5.00E-5	90
41	1.00E-4	34
42	1.00E-4	86
43	1.00E-4	36
44	1.00E-4	82
45	5.00E-5	100
46	5.00E-4	100

Additionally selected intermediates of the present invention also provide inhibition in the glycine-binding assay as follows:

TABLE II

Preparation No.	Molar Conc.	% Inhibition
1	1.11E-4	30
2	1.00E-4	6
3	1.00E-4	97
5	1.00E-4	88
6	1.00E-4	10
7	1.00E-4	13
8	1.00E-4	0
9	1.00E-4	74
10	1.00E-4	65
11	1.00E-4	23

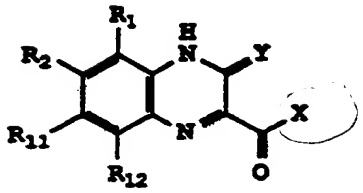
The AMPA binding assay may also be performed to provide an activity profile for the compounds of the present invention.

The kainate binding assay is performed as described by T. Honore et al, Neuroscience Letters 1986;65:47-52.

Therefore, the compounds of Formula I and their pharmacologically acceptable acid addition salts are effective agents in the prophylaxis and/or therapeutic treatment of disorders responsive to agents which block NMDA receptors, thus forming a further aspect of the present invention in like manner.

CLAIMS

1. A compound of the formula



I

or a pharmaceutically acceptable base or acid addition salt thereof; wherein

(1) Y is oxygen or sulfur;

(2) R_1, R_2, R_{11}, and R_{12} are independently hydrogen, lower alkyl, halogen, trifluoromethyl, cyano, nitro, methylthio, lower alkenyl, lower alkynyl, SO_2NH_2, $S(O)_{1-2}R$ wherein R is hydrogen or lower alkyl, OCF_3, or two of R_1, R_2, R_{11}, and R_{12} can be taken together to form a carbocyclic ring of six carbons, or can be taken together to form a heterocyclic or heteroaryl ring wherein the heteroatom is oxygen, sulfur, or nitrogen, and wherein the carbon on the carbocyclic ring is optionally further substituted by one of R_1, R_2, R_{11}, or R_{12};

(3) X is

(a) $NR^6SO_2R^3$,

(b) NR^6R^3 with the proviso that one of R^6 and R^3 must be other than hydrogen and at the same time one of R_1, R_2, R_{11}, and R_{12} must be other than hydrogen,

(c) NR^6OR^3,

(d) $NR^6CONR^3R^4$ with the proviso that one of R^3 and R^4 must be other than hydrogen,

(e) NR^6COR^5,

(f) $NR^6CO_2R^3$,

(g) $N(R^6H)-N-CO_2R^3$

(h) $N(R^6H)-N-SO_2R^3$

(i) an amino acid residue which is phenylglycine, phenylalanine, alanine, leucine, isoleucine, proline, or valine,

(j) lower alkyl esters of the amino acid residue as defined above;

wherein

i) R^3 and R^4 are independently

1) hydrogen;

2) alkyl of from one to twenty carbons, preferably one to twelve carbons;

3) alkenyl of from three to twenty carbons, preferably three to twelve carbons;

4) alkynyl of from three to twenty carbons, preferably three to twelve carbons;

5) aryl which is phenyl, indenyl, or naphthyl wherein phenyl is

aa) unsubstituted or

bb) substituted by one to five of lower alkyl or halogen, or

cc) substituted by one to three of

xxi) trifluoromethyl,

xxii) nitro,

xxiii) amino,

xxiv) mono- or di-lower alkylamino,
xxv) hydroxy,
xxvi) lower alkoxy,
xxvii) carboxy, or
xxviii) $NHCOR^5$ wherein R^5 is independently as defined below,

xxix) $NHCOAlk_{1-6}$ wherein Alk_{1-6} is lower alkyl,
xxx) $NHSO_2R^5$ wherein R^5 is independently as defined herein,
xxxi) CN,
xxxii) $CONR^5R^6$ wherein R^5 and R^6 are independently as defined herein,
xxxiii) $S(O)_{0-2}R^5$ wherein R^5 is independently defined herein,

xxxiv) $-CR^5$;

6) arylloweralkyl;
7) arylloweralkenyl;
8) heterocycle;
9) heteroaryl;
10) $(CH_2)_qR^7$ wherein q is an integer of one to four and R^7 is
(A) heterocycle,
(B) heteroaryl,
(C) SO_2R^8 wherein R^8 is hydrogen or lower alkyl and R

is independently as defined herein,

(D) PO_3R^8 wherein R^8 is as defined above,

(E) CO_2R^8 wherein R^8 is as defined above, or

(F) NR^9R^{10} wherein R^9 and R^{10} are independently hydrogen or alkyl or R^9 and R^{10} are taken together to form a heteroaryl ring; or

11) an amino acid residue as defined above;

ii) R^5 is

1) hydrogen,
2) lower alkyl,
3) lower alkenyl,
4) aryl,
5) arylloweralkyl,
6) arylloweralkenyl,
7) heteroaryl or
8) heteroarylloweralkyl;

iii) R^6 is

1) hydrogen or
2) lower alkyl, preferably hydrogen.

2. A compound of Claim 1 wherein R_1 and R_{12} are hydrogen and R_2 and R_{11} are chloro.

3. A compound of Claim 1 wherein X is $NR^6SO_2R^3$.

4. A compound of Claim 1 wherein X is NR^6R^3.

5. A compound of Claim 1 wherein X is NR^6OR^3.

6. A compound of Claim 1 wherein X is $NR^6CONR^3R^4$.

7. A compound of Claim 1 wherein X is NR^6COR^5.

8. A compound of Claim 1 wherein X is $NR^6CO_2R^3$.

9. A compound of Claim 1 wherein X is $NHNHSO_2R^3$.

10. A compound of Claim 1 wherein X is $NHNHCO_2R^3$.

11. A compound of Claim 4 which is α-[[6,7-dichloro-3,4-dihydro-3-oxo-2-quinoxalinyl]carbonyl]amino-(±)-benzeneacetic acid.

12. A compound of Claim 3 which is 6,7-dichloro-3,4-dihydro-N-(methylsulfonyl)-3-oxo-2-quinoxaline-carboxamide.

13. A compound of Claim 3 which is 6,7-dichloro-3,4-dihydro-3-oxo-N-(phenylsulfonyl)-2-quinoxaline-carboxamide.

14. A compound of Claim 3 which is N-(butylsulfonyl)-6,7-dichloro-3,4-dihydro-3-oxo-2-quinoxaline-carboxamide.

15. A compound of Claim 3 which is 6,7-dichloro-3,4-dihydro-N-[(4-methylphenyl)sulfonyl]-3-oxo-2-quinoxalinecarboxamide.

16. A compound of Claim 3 which is 6,7-dichloro-3,4-dihydro-N-[(2-chloro-5-nitrophenyl)sulfonyl]-3-oxo-2-quinoxalinecarboxamide.

17. A compound of Claim 3 which is 6,7-dichloro-N-[(4-chloro-2-nitrophenyl)sulfonyl]-3,4-dihydro-3-oxo-2-quinoxalinecarboxamide.

18. A compound of Claim 3 which is 6,7-dichloro-3,4-dihydro-N-(2-thionylsulfonyl)-3-oxo-2-quinoxalinecarboxamide.

19. A compound of Claim 3 which is 6,7-dichloro-3,4-dihydro-N-[(4-methoxyphenyl)sulfonyl]-3-oxo-2-quinoxalinecarboxamide.

20. A compound of Claim 3 which is 6,7-dichloro-3,4-dihydro-3-oxo-N-[[5-(2-pyridinyl)-2-thienyl]-sulfonyl]-2-quinoxalinecarboxamide.

21. A compound of Claim 3 which is 6,7-dichloro-3,4-dihydro-N-[(3-chlorophenyl)sulfonyl]-3-oxo-2-quinoxalinecarboxamide.

22. A compound of Claim 3 which is 6,7-dichloro-3,4-dihydro-3-oxo-N-[(3-nitrophenyl)sulfonyl]-2-quinoxalinecarboxamide.

23. A compound of Claim 3 which is 6,8-dichloro-3,4-dihydro-N-(methylsulfonyl)-3-oxo-2-quinoxaline-carboxamide.

24. A compound of Claim 3 which is 6,8-dichloro-3,4-dihydro-3-oxo-N-phenylsulfonyl)-2-quinoxaline-carboxamide.

25. A pharmaceutical composition comprising a therapeutically effective amount of a compound of

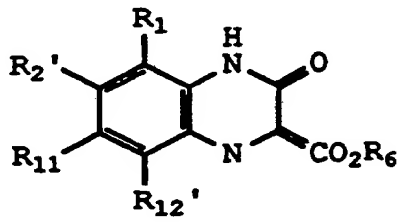
Claim 1 together with a pharmaceutically acceptable carrier.

26. A method for treating cerebrovascular disorders which comprises administering to a patient in need thereof the pharmaceutical composition of Claim 25 in unit dosage form.

27. A method for treating disorders responsive to the blockade of glutamic and aspartic acid receptors which comprises administering to a patient in need thereof the pharmaceutical composition of Claim 25 in unit dosage form.

28. A method for treating stroke which comprises administering to a patient in need thereof the pharmaceutical composition of Claim 26 in unit dosage form.

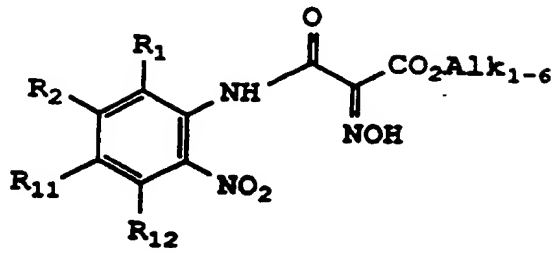
29. A pure compound of the Formula XII



XII

R_1 and R_{11} are defined above in Claim 1 and R_6 is hydrogen or lower alkyl and R'_2 and R'_{12} are independently halogen or hydrogen with the proviso that one of R'_2 and R'_{12} is halogen.

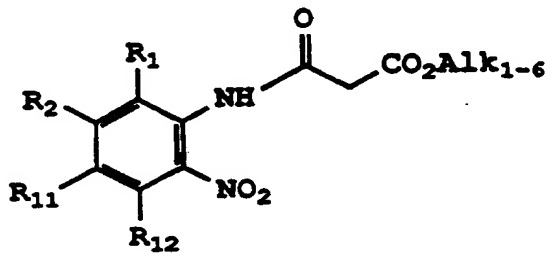
30. A compound of the formula (V)



V

wherein R_1, R_2, R_{11}, and R_{12} are as defined in Claim 1 and Alk_{1-6} is lower alkyl.

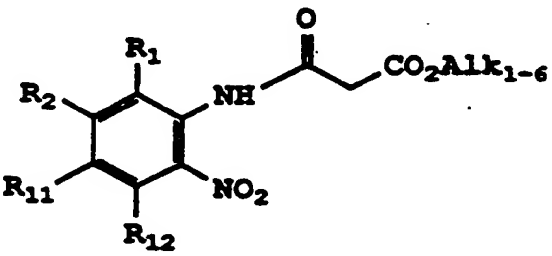
31. A compound of the Formula (VI)



VI

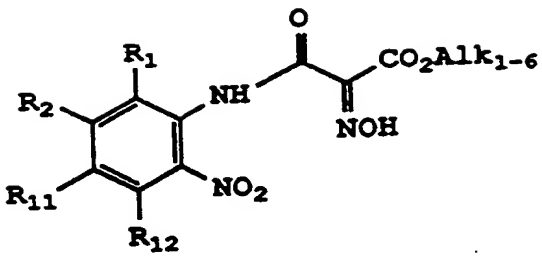
wherein R_1, R_2, R_{11}, and R_{12} are as defined in Claim 1 and Alk_{1-6} is lower alkyl.

32. A method of 1) treating a compound of the Formula (VI)



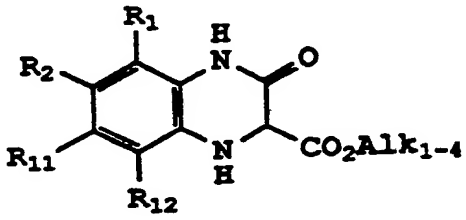
VI

with sodium nitrite to obtain a compound of the Formula (V)



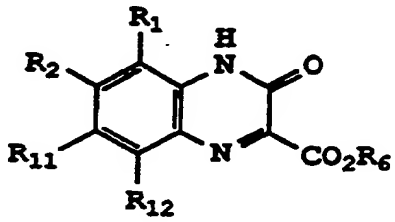
V

then 2) treating the compound of the Formula II'$_2$ with hydrogen over Raney nickel followed by treatment with $TiCl_3$ to obtain a compound of the Formula (IV)



IV

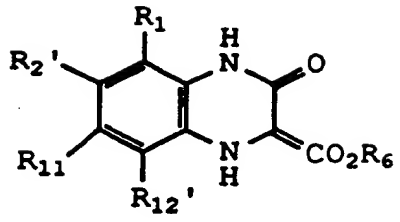
with the compound of the Formula IV further 3) reacted with Br_2, n-bromosuccinimide, NaOCl, or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone and alternatively saponifying this product to obtain the compound of the Formula (II)



II

wherein R_1, R_2, R_{11}, R_{12}, and R_6 are as defined in Claim 1.

33. A pure compound of the Formula (XIII)



XIII

wherein R_1, R'_2, R_{11}, R'_{12}, and R_6 are as defined in Claim 29.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 91/08586

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 241/44 C 07 D 401/04 C 07 C 233/54
C 07 C 251/38 A 61 K 31/495

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D 241/00 C 07 D 401/00 C 07 C 233/00 C 07 C 251/00 A 61 K 31/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	EP,A,0008864 (FISONS LTD) 19 March 1980, see claims 1,5,8,9	1,25,32
A	EP,A,0010426 (ELI LILLY AND CO.) 30 April 1980, see claims 1,4,6 (cited in the application)	1,25,32
A	US,A,4252954 (ABDULLA et al.) 24 February 1981, see claims 1,8 (cited in the application)	1,25
A	US,A,4264600 (ABDULLA) 28 April 1981, see claim 1, reaction schemes 1,2 (cited in the application)	1,25,30 ,32

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
18-02-1992	31. 03. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Miss T. MORTENSEN

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claim numbers 26-28 because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): method for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. [ ] Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the International application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANHANG
zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

ANNEX
to the International Search Report to the International Patent Application No.

ANNEXE
au rapport de recherche international relatif á la demande de brevet international n°

PCT/US91/08586 SAE 54229

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

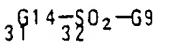
This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The Office is in no way liable for these particulars which are given merely for the purpose of information.

La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche international visée ci-dessus. Les reseignements fournis sont donnés á titre indicatif et n'engagent pas la responsibilité de l'Office.

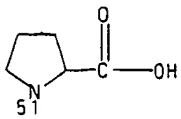
Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
EP-A1- 8864	19-03-80	AU-A1-49853/79	21-02-80
		DK-A - 3383/79	16-02-80
		ES-A1- 483398	01-09-80
		FI-A - 792507	16-02-80
		IL-A0- 58038	30-12-79
		JP-A2-55115875	06-09-80
		NO-A - 792653	18-02-80
		PT-A - 70064	01-08-79
		US-A - 4296114	20-10-81
		ZA-A - 7904209	30-07-80
		GB-A1- 2037591	16-07-80
EP-A1- 10426	30-04-80	AU-A1-51977/79	01-05-80
		BE-A1- 879472	18-04-80
		CA-A1- 1145337	26-04-83
		DD- C- 146705	25-02-81
		ES-A1- 485221	01-07-80
		ES-A5- 485221	01-08-80
		ES-A1- 485222	01-09-80
		FI-A - 793261	21-04-80
		IT-A0- 7926662	19-10-79
		PT-A - 70340	01-10-79
		DK-A - 4444/79	21-04-80
		EP-A1- 10426	30-04-80
		FR-A1- 2439188	16-05-80
		FR-A1- 2448899	12-09-80
		GB-A1- 2034302	04-06-80
		IL-A0- 58478	31-01-80
		IT-A - 1193847	24-08-88
		JP-A2-55069514	26-05-80
		LU-A - 81798	21-04-80
		PH-A - 15791	25-03-83
		PL-A1- 221591	10-07-81
		RO- P- 78225	01-02-82
		DK-A - 4444/79	21-04-80
		FR-A1- 2439188	16-05-80
		FR-A1- 2448899	12-09-80
		GB-A1- 2034302	04-06-80
		IL-A0- 58478	31-01-80
		IT-A - 1193847	24-08-88
		JP-A2-55069514	26-05-80
		LU-A - 81798	21-04-80
		PH-A - 15791	25-03-83
		RO- P- 78225	01-02-82
		ZA-A - 7905491	27-05-81
		US-A - 4264600	28-04-81
US-A - 4252954	24-02-81	AU-A1-63512/80	30-04-81
		BE-A1- 885793	21-04-81
		CA-A1- 1149381	05-07-83
		CS- P- 212304	26-03-82
		DD- C- 153689	27-01-82
		DK-A - 4497/80	26-04-81
		EP-A1- 29658	03-06-81
		ES-A1- 496210	01-10-81
		ES-A1- 8205207	16-09-82
		FI-A - 803294	26-04-81
		FR-A1- 2467848	30-04-81
		GB-A1- 2061936	20-05-81
		IL-A0- 61313	31-12-80

		IT-A0- 8025538	23-10-80
		IT-A - 1134009	24-07-86
		JP-A2-56081569	03-07-81
		PL-A1- 227421	19-06-81
		PT-A - 71939	01-10-80
		PT-B - 71939	31-08-81
		YU-A - 2688/80	28-02-83
		ZA-A - 8006437	26-05-82
US-A - 4264600	28-04-81	AU-A1-51977/79	01-05-80
		BE-A1- 879472	18-04-80
		CA-A1- 1145337	26-04-83
		DD- C- 146705	25-02-81
		DK-A - 4444/79	21-04-80
		EP-A1- 10426	30-04-80
		ES-A1- 485221	01-07-80
		ES-A5- 485221	01-08-80
		ES-A1- 485222	01-09-80
		FI-A - 793261	21-04-80
		FR-A1- 2439188	16-05-80
		FR-A1- 2448899	12-09-80
		GB-A1- 2034302	04-06-80
		IL-A0- 58478	31-01-80
		IT-A0- 7926662	19-10-79
		IT-A - 1193847	24-08-88
		JP-A2-55069514	26-05-80
		LU-A - 81798	21-04-80
		PH-A - 15791	25-03-83
		PT-A - 70340	01-10-79
		RO- P- 78225	01-02-82
		ZA-A - 7905491	27-05-81
		DK-A - 4444/79	21-04-80
		EP-A1- 10426	30-04-80
		FR-A1- 2439188	16-05-80
		FR-A1- 2448899	12-09-80
		GB-A1- 2034302	04-06-80
		IL-A0- 58478	31-01-80
		IT-A - 1193847	24-08-88
		JP-A2-55069514	26-05-80
		LU-A - 81798	21-04-80
		PH-A - 15791	25-03-83
		PL-A1- 221591	10-07-81
		RO- P- 78225	01-02-82

G6 = 31



G9 = 51



DER: or pharmaceutically acceptable base or acid addition salts
MPL: claim 1

****

AN 118:101927 MARPAT

TI Preparation of N-arylsulfonyl-3,4-dihydro-3-oxo-quinoxaline-2-carboxamides and analogs as neuroprotectants

IN Hays, Sheryl Jeanne; Johnson, Graham; Lescosky, Leonard Joseph; Malone, Thomas Charles; Novak, Perry Michael

PA Warner-Lambert Co., USA

SO PCT Int. Appl., 104 pp.
CODEN: PIXXD2

PI WO9211245 A1 920709

DS W: AU, CA, FI, JP, KR, NO, US
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE

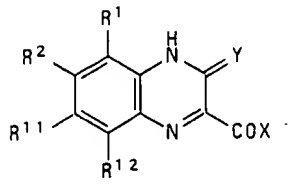
AI 91WO-US08586 911122

PRAI 90US-0631139 901220

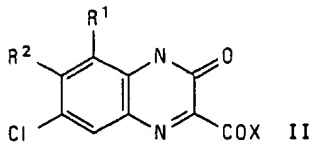
DT Patent

LA English

GI



I



II

AB Title compds. (I; R^1,R^2,R^{11},R^{12} = H, alkyl, halo, CF_3, cyano, etc.; X = $NR^6SO_2R^3$, NR^6R^3, NR^6OR^3, etc.; R^3 = H, alkyl, alkenyl, aryl, etc.; R^6 = H, alkyl; Y = O, S) were prepd. Thus, 4,6-dichloro-2-nitroaniline was condensed with $ClCOCH_2CO_2Et$ and the product cyclized to give, after PCl_3 treatment of the N-oxide and sapon. quinoxalinecarboxylate **II** (R^1 = Cl, R^2 = H) (**III**; X = OH) which was condensed with $PhSO_2NH_2$ to give **III** (X = $NHSO_2Ph$). **II** (R^1 = H, R^2 = Cl, X = $NHSO_2R^3$,R^3 = 1*H*-inden-5-yl) gave 100% inhibition of glycine binding at NMDA receptors at 5.00 × 10^{-5} M in vitro.

MSTR 1A